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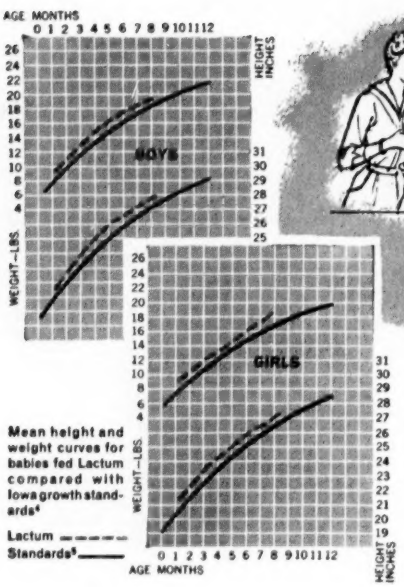

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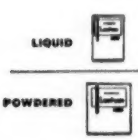

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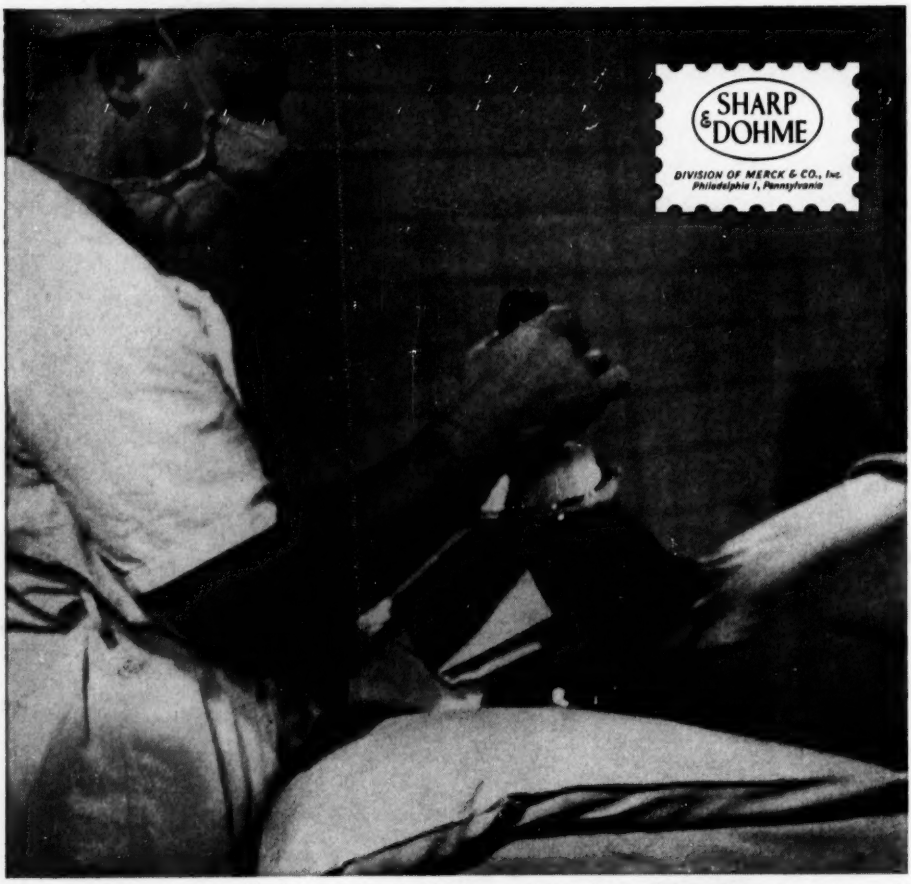

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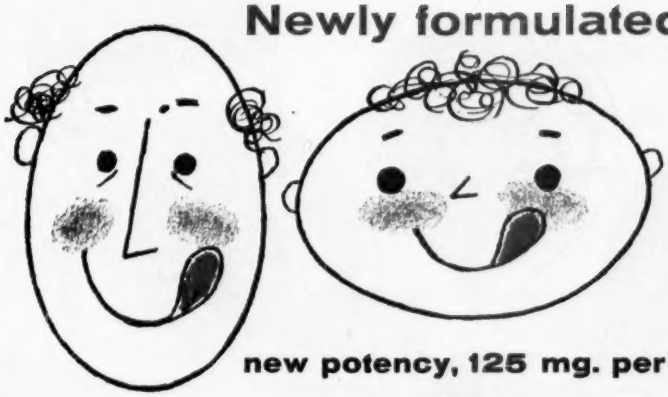

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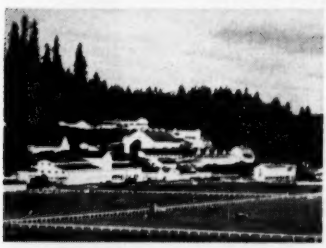

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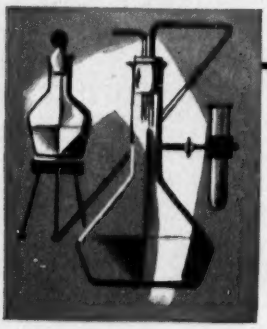

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RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE IN CHILDREN AS SEEN IN CLINIC PRACTICE

I. Clinic Diagnostic Technique

LINDON L. DAVIS, M.D.
WILLISTON PARK, N. Y.
AND
MARJORIE H. GREENE, M.D.
LEVITTOWN, N. Y.

IT IS GENERALLY conceded that in the many cardiac clinics rheumatic heart disease is frequently overdiagnosed and underdiagnosed. The fact that this situation obtains is evidence of the inadequacy of the present diagnostic criteria used in most clinics. It is evident that the clinical manifestations of rheumatic fever have undergone a vast change of character. The magnitude of the shift is perhaps not generally appreciated and is not reflected in the textbook descriptions of rheumatic fever.[1] These continue to describe classic attacks of rheumatic fever in terms of polyarthritis, fever, elevated sedimentation rate, arthralgias, and prolonged P-R intervals. In our experience and in the experience of most students of rheumatic fever, these cases are now rarely encountered. Major and minor criteria,[2] when present, are of utmost diagnostic importance, but these are absent in the great majority of cases seen in the clinic. The "typical" case, in our experience, has no explosive attack and few or none of the orthodox classic manifestations.[3] Often, in fact, the parents are unaware that the child is ill. The patient sees the physician for some minor complaint, such as pallor, fatigue, emotional disturbance, or poor eating or sleeping habits, and on examination presents abnormal cardiac findings. Frequently, it is only after repeated examinations that a diagnosis of carditis is made, and the child's symptoms may remain unnoticed unless the parents are questioned minutely. When the cases are considered from an over-all point of view, one sees that the outstanding manifestation of the disease process is carditis, frequently smoldering in nature. In many cases the carditis is so mild as to render diagnosis most difficult and immediate determination of activity of the disease almost impossible. This is the type of case that remains undiagnosed until obvious and irreparable total cardiac damage has occurred.[4] Ten- and 20-year studies of these patients assure us that many have had carditis, despite the absence of diagnostic signs and symptoms.* Dr. Rutstein's studies indicate clearly that there is a wide variation in the state of New York (from 0 to 13%) in the diagnosis of rheumatic disease by the general practitioner in comparable groups of children. Initial examination of cardiac patients in excellent clinics by experts on the rheumatic diseases resulted in one-third of the persons examined being classified as

From the Rheumatic Heart Clinic, Meadowbrook Hospital, East Meadow, Long Island, N. Y.

* References 5, 6, and 7.

having possible and/or potential heart disease.[8] Our figures are comparable to this. These considerations, in our opinion, form the background for the many conflicting concepts relating to the natural history of rheumatic fever. Some investigators are content to recognize the disease only where it manifests the classic exudative phenomena. Others feel that the patient with smoldering carditis is the commonest and, therefore, the case typifying the disease. In this communication, we are concerned with the second group of cases, since these constitute a formidable problem in diagnosis.

The children seen at the diagnostic rheumatic fever clinic at Meadowbrook Hospital represent a selected group who fall into this category. They are referred to this clinic by the family physician for evaluation of puzzling cardiac findings or questionable rheumatic symptomatology. As might be expected, classic cases of rheumatic fever are not sent to the clinic, and illnesses of other etiology have, for the most part, been screened out. Known cases of rheumatic heart disease and congenital heart disease are also followed in the clinic on request of the family physician. Out of 141,793 school children in Nassau County in the school year 1951-1952, there were 306 who were sent to this clinic. The processing of such a selected group each year through a clinic staffed by careful and competent observers should, we feel, provide material worthy of study. It is the immediate purpose of this study to present an analysis of the total numbers of cases surveyed during the years 1951-1952. It is, further, our purpose to present a diagnostic technique and diagnostic criteria found to be most helpful in our rheumatic fever clinic.

CLINIC ROUTINE

The cardiac clinic at Meadowbrook Hospital is run as a consultation service for school children of limited means in Nassau County. When a child is referred to the clinic, a standard information form is filled out by the school physician. An appointment is made for the child, who, together with the parents, is brought from home to the clinic by automobile. The parents and children are first seen by the social service department for an interview, then by a nurse, and then by the doctor. The routine for examination is first, physical examination by the doctor, then laboratory work in the following order: blood cell count, urinalysis, electrocardiography, and x-ray, with barium swallow; occasionally electrocardiography is the last procedure. Fluoroscopy is done by the x-ray department if requested. The x-rays are reviewed by the examiner. The child returns to the clinic one week later for reexamination and final evaluation. Reports of the work done at the clinic are sent to the family physician and the school physician, together with any recommendation for therapy or follow-up work. Blood cell counts and urinalyses are done in the Meadowbrook Hospital laboratory. X-rays are read by one of two radiologists. Electrocardiograms are all read by both of us, and all Q-T_e's are read by one of us (M. H. G.).† The history, physical examinations, and diagnosis are recorded on charts provided by the American Heart Association. The diagnosis is recorded in accordance with the recommendations in the "Nomenclature and Criteria for Diagnosis of Diseases of the Heart."[9]

† The method used in reading and deriving the Q-T_e is that described by Taran and Szilagyi.[13]

ANALYSIS OF CASES

During the clinic year 1951-1952, a total of 306 school children were seen (Table 1). In this group, two out of every three patients surveyed did not present sufficient evidence upon which to make a diagnosis of heart disease or suspected heart disease. More than one-third of this group presented clinical evidence which dictated the diagnosis of possible heart disease [9] or had a history which predicated the possibility that rheumatic heart disease might develop in the future. These cases were therefore defined as potential heart diseases.[9] More than 10% of the group had congenital heart disease, and almost 1 out of every 10 children presented unequivocal evidence of rheumatic heart disease. It is noteworthy that only one of the group of rheumatic children was found to have definite acute rheumatic heart disease.

PROBLEMS IN DIAGNOSIS

1. *Presenting Symptomatology.*—It is important to emphasize that this clinic does not see the general run of pediatric or cardiac patients. The usual case sent for evaluation is representative of that most difficult group of pediatric patients, those in whom something wrong is suspected but who present no clear diagnostic

TABLE 1.—*Children Seen at the Cardiac Clinic of Meadowbrook Hospital During 1951-1952*

Total Cases	No Heart Disease		Possible and Potential Heart Disease		Definite Heart Disease			
					Congenital		Rheumatic	
	No.	%	No.	%	No.	%	No.	%
306	120	41.1	115	37.3	36	11.7	29	9.4

signs. These children, as is well known, must sometimes be followed for many months before definite diagnosis can be made. This situation is exemplified by the following case histories:

J. G., a 12-year-old girl, was first seen in April, with a history of low-grade fever for two days, slight cough, malaise, and a past history of bronchopneumonia (three times) and hives. Her maternal grandfather had heart disease of undetermined etiology, and the father had bronchial asthma. Physical examination was within normal limits, and the same was true of x-ray. The electrocardiogram had notched P waves in Leads I and aV_L. $Q\text{-}T_c$ was 0.425. The final diagnosis was potential heart disease. The patient returned to the clinic in seven months, at which time her findings were reevaluated, and a diagnosis of no heart disease was made.

H. K., a 7-year-old girl, was presented to the clinic with a history of low-grade fever intermittently over a six-month period, pallor, and fatigue. One and one-half and two years ago, she had had muscle pains, joint pains, and "growing pains." Other than that there had been only measles and whooping cough in the past. Family history was negative for either rheumatic fever or cardiac disease of any kind. The only positive physical findings were a low-pitched Grade II murmur at the mitral area and a pulmonic second sound greater than the aortic second sound. Hemoglobin was 10.4 gm. per 100 cc., and the vital capacity was —30%. All other data, including the x-ray and electrocardiogram, were within normal limits, and the child was discharged from the clinic with a diagnosis of no heart disease. The following month the findings were the same, but a diagnosis of potential heart disease was made. Five months after the first visit, the child was again examined, and the physical findings were essentially unchanged, but x-ray of the chest showed the pulmonary artery segment to be somewhat enlarged, and there was a prominence of the bronchovascular markings. $Q\text{-}T_c$ at this time was 0.422. The vital capacity was normal. At this time the complete diagnosis was active rheumatic heart disease, enlarged heart, mitral insufficiency, regular sinus, rhythm, 1A.

Careful study of these two cases shows the vague character of the presenting histories and the absence of clear-cut physical findings. In the second case, it is apparent that rheumatic carditis had been present and active when all clinical and laboratory signs were negative. There is considerable similarity in these two cases, and yet the diagnosis derived is quite different. Careful analysis of the average child's history in our clinic is of this type.

2. *Clinic Technique.*—In any clinic, a child will in all probability be seen by several different observers. The manner in which the physical examniation and work-up are done and recorded, then, becomes of paramount importance for two reasons: (*a*) that the variables of technique and patient response be reduced to a minimum, and (*b*) that results be recorded in a standard manner, so as to admit of exact interpretation by another doctor. It would seem necessary that the doctors who work together in a clinic meet at least once every two or three months to discuss uniform grading and recording of heart sounds and murmurs, methods and techniques in history taking, physical examination, and interpretation of abnormalities on the electrocardiogram, and the evaluation of cardiac fluoroscopy with barium swallow. We feel so strongly on the above points that we wish to set down our requirements for such a clinic, in comparison with methods obtaining at present.

On visiting the clinic, the child should be separated from the parents and be accompanied by a sympathetic nurse, who will stay with the child throughout his entire sojourn at the clinic, both on the present and on succeeding visits. The excitement and apprehension of the parents are too often transmitted to the child, whose nervousness is thereby increased to even greater proportions. While the nurse and child are becoming acquainted and the child is resting on the examining table, the physician who is to see the child is in a separate room taking a detailed history from the parents concerning the child's everyday life. Specific inquiry should be made with regard to (1) loss of time from school, (2) nosebleeds, (3) undue fatigue, (4) muscle and joint pains, (5) capricious appetite, (6) withdrawal from active play, (7) behavior changes, (8) restless sleep, and (9) pallor. The past history must also be carefuly searched for the above symptomatology and for a record of previous illnesses, with special emphasis on scarlet fever, chorea, rheumatic fever, or frequent sore throats of streptococcal origin. Frequently, parental memory is inadequate to the extent that loss of time from school is the best standard for judging the general health of the child. One must frequently be quite specific and exacting with the parents in order to extract information about the child's behavior pattern definite enough to be of value.

A family history of heart disease is a point worth the doctor's time. Any heart disease mentioned by the parents should be inquired into carefully. The history of heart disease in the immediate family should be confirmed by an examination of the person in question.‡ The occurrence of rheumatic heart disease in other members of the immediate family is of definite value.

When this has been accomplished, the physician should proceed with the physical examination, allowing several minutes of light conversation with the child and nurse in order to further allay the child's apprehension. At this time, a cursory examination of the precordium should be done in order to acquaint the physician

‡ References 10 and 11.

with the heart sounds, rate, murmurs, and thrills, if present. Then, careful and complete physical examination should be done, with the examination of the heart following the routine here outlined:

1. The chest is inspected for precordial thrust or thoracic deformities.

2. The chest is palpated for the heart thrust, apical beat, and thrills. If the latter are present, they should be recorded as the time in the cycle, duration, intensity, and location on the chest wall.

3. Percussion has not been found to be of help in diagnosis in our experience.

4. On auscultation, the heart sounds themselves should be carefully studied and any abnormality recorded. Any murmurs that are present should be recorded as to pitch, quality, duration, location, and intensity and according to Levine's classification as to grade.[12]

The above examination should be carried out in the usual three positions for cardiac ausculation and after exercise. Graphic, accurate, and uniform recording of the cardiac findings is of utmost importance so that other physicians can easily interpret the previous examination.

On the first visit to the clinic, the child should be seen by only one physician. On completion of the physical examination, the child should remain in the same room to have an electrocardiogram. Here, technique is of the greatest importance. The patient should be allowed to lie quietly while the technicians become acquainted with him and, meanwhile, explain the procedure to him. At no time must he feel that there is anything hurried about taking the "picture," and in many instances if the child is encouraged to close his eyes he relaxes more completely and the tracing has less tremor. Since we follow the method of Taran and Szilagyi,[13] it is to be noted that the child has not been given drugs of any sort, including acetylsalicylic acid, before the tracing is taken. The three limb leads, the augmented limb leads, and six V leads are taken, and the Q-T_c is measured by taking the longest and shortest cycle in each of six leads. Leads I, II, III, and V_2, V_4, and V_5, measuring the Q-T and cycle length, and computing the average by Bazett's formula, $Q\text{-}T_c = \frac{Q\text{-}T}{R\text{-}R}$.

After this, the vital capacity should be measured, if possible by the same technicians, thus reducing the number of new people to whom the child must become accustomed.[14]

Next, fluoroscopy is done by the child's own physician. Any good fluoroscopic technique is acceptable. Many examiners are not well trained in cardiac fluoroscopy, a natural result of the frequently found separation of the x-ray department from the clinic, both physically and in spirit. A uniform technique and procedure should be followed, with exact methods and standards of interpretation set up by the group. The following standards are suggested (Table 2).

Immediately after this examination, 6 ft. chest x-rays are taken in the three positions for a permanent record. Any other laboratory procedures, such as determination of sedimentation rate, complete blood cell count, and urinalysis, would be done only at the discretion of the examining physician.

On returning to the clinic, the patient again sees the same nurse and physician and is reexamined, and the findings are reevaluated in conjunction with the laboratory data. If there is somatic tremor or marked tachycardia, the electrocardiogram should be repeated every week until the examiner feels that the patient is sufficiently at ease that the findings on the tracing can be interpreted as basal. The same is true of a markedly low vital capacity. When all examinations and evaluations by the

TABLE 2.—*Suggested Standards of Interpretation of Fluoroscopic Examination*

Extent of Enlargement	Posteroanterior View		Right Antero-oblique Esophogram	Left Antero-oblique	
	Left Ventricle	Pulmonic Segment		Left Ventricle Angle of Clearance, Degrees	Right Ventricle
1—Minimal	Apex located at a point 50-75% of the left chest diameter	Straightening of left border	Slight general backward displacement	55-65	General smooth bulging of the right border
2—Moderate	Apex located at a point 75-100% of the left chest diameter	Pulmonary segment, convex	Definite special segment displacement	65-75	Definite right ventricular shelf
3—Marked	Apex in contact with chest wall, which separates from it on deep inspiration	Convex pulmonary segment does not peak on inspiration	Displacement of esophagus and narrowing	75-90	Marked shelf, heart border does not touch chest wall
4—Maximum	Chest wall does not separate from apex on deep inspiration	Marked point of pulmonary segment	Marked displacement of esophagus, with delay in passage of barium	Does not clear	Marked shelf, with heart border at chest wall

examining physician have been completed, the child is presented for further evaluation by other members of the clinic staff and a final diagnosis is recorded, with a note suggesting the disposition of the case.

3. *Scale Of Measurement Of Diagnostic Criteria.*—Our criteria are discussed here with the thought of following the pattern of the doctor's examination at the clinic for the purpose of diagnosis of rheumatic heart disease without reference to present activity. This subject of activity will be dealt with in a subsequent paper.

Any of the symptoms referred to in the history may be without relation to heart disease, but should one or several symptoms indicative of heart disease be present, the physician will place them on the positive side of the scale. Any heart disease mentioned by the parent during the history should be carefully and minutely screened, particularly if the etiology is obscure, to determine whether it might be rheumatic. The occurence of rheumatic heart disease in other members of the immediate family is of definite positive value, and rheumatic fever in both parents is a point of great positive diagnostic value. Should both parents have rheumatic heart disease and the child be found to be completely negative on examination, the case should be diagnosed as potential heart disease, and the child should be followed until his rheumatic fever becomes evident.§

General inspection of the child usually yields our most telling diagnostic information. In our opinion, marked pallor may be the first noticed physical finding. This clue is often the first and most important one pointing to the presence of acute heart disease. Should the child have other general signs of heart disease, such as shortness of breath, cyanosis, or venous engorgement, the patient no longer presents a problem in the diagnosis of heart disease, but rather a problem in classification as to the type of heart disease and the disposition of the case. Subcutaneous nodules are rarely encountered in our clinic, perhaps because of the select group of patients. The skin should be carefully inspected for erythematous rash. An erythema marginatum is helpful, not only in diagnosis but also as a point in evaluating activity of rheumatic fever.

The finding of a few scattered rales and/or wheezy breath sounds of nondescript nature in the chest may be regarded as positive points of rather small diagnostic value. In a known case of rheumatic heart disease, these sounds frequently may be indicative of rheumatic disease of the lungs. A precordial bulge, a heaving impulse, or a forceful apex beat point directly to abnormality of the heart, but not specifically to rheumatic heart disease. A systolic thrill at the apex is frequently confusing and often misdiagnosed but is helpful in diagnosing rheumatic heart disease.

AUSCULTATION

In this part of the examination, the doctor should be most specific about his findings, as previously suggested. The rhythm may be that of a normal quiet heart. If it is hurried, one must assess the emotional state of the child at the moment in an attempt to determine whether the rhythm is out of keeping with the placidity of the patient. If the heart rate is less than 90 with the child fairly at ease and the rhythm is metronomic or tumultuous, there can be no question that the heart is

§ References 10 and 11.

overactive. Heart disease is present, although the etiology remains to be determined. The examiner's attention is next directed to the character of the heart sounds. The mitral first sound is found to be louder than the mitral second sound in early mitral stenosis and also in many nonrheumatic conditions in which the blood velocity is increased. A mitral first sound of less intensity than a mitral second sound is indicative of a prolonged P-R interval. This will receive comment later, with other electrocardiographic findings. A loud snapping or reduplicated pulmonic second sound is on the positive side of the diagnostic scale. Care must be taken to differentiate third heart sounds from small middiastolic murmurs.

If no murmurs are found, the remainder of the physical examination can hardly be expected to produce much of assistance, inasmuch as in our diagnostic clinic for children we do not expect to find advanced heart disease.‖ Murmurs, we believe, should be recorded in great detail in any manner agreed upon by the doctors of the clinic. We have found practical the method suggested at St. Francis Sanatorium for Cardiac Children.[15] Should one hear at the apex a harsh systolic murmur of Grade 3 or greater intensity, of decrescendo type, filling most of the systole, and should this be the only abnormal sound heard, a diagnosis of rheumatic heart disease may be made. This diagnosis may also be made when the only abnormal sounds heard consist of a systolic and diastolic murmur, of whatever intensity, at the apex. The above statement indicates that a diagnosis of rheumatic heart disease can be made when a systolic murmur of a certain character and of a certain loudness is detected, even if it is the only abnormal finding discovered on examination. Indeed, it may well be true of an apical systolic murmur of 2 + intensity, but our present experience, and the cases in the literature which have been well followed, are not of sufficiently impressive nature as to allow such a statement to go uncontested.¶ It has been the experience of one of us to have made a diagnosis of rheumatic heart disease on a teen-age girl with a tumultuous heart and a Grade 3 to 4 systolic murmur at the apex, as described above, and no other abnormal findings. At autopsy, the diagnosis of Fiedler's myocarditis was made. We do not believe that the occurrence of a rare exception should make it necessary to abandon this diagnostic principle. One should be aware from history or physical examination whether the child has one of the acute childhood infections or an anemia of any considerable degree, and one should not attempt to apply this principle to such a case. Having repeatedly stated with varying phraseology that the examiner should not fall into this difficulty, we feel that the point has been made. An attempt to make a diagnosis of rheumatic heart disease on the basis of murmurs heard at areas other than the apex brings the examiner directly to the problem of congenital heart disease. The more recent techniques of angiocardiography and cardiac catheterization have produced considerable literature offering the opportunity to compare heart sounds and murmurs with known congenital defects. The variability of murmurs in the common defects is of the order of 0 to 5 + and presents diagnostic problems beyond the scope of this paper.#

‖ References 8 and 9.

¶ References 5, 7, and 21-24.

References 16-19.

A vital capacity which is properly measured, rechecked, and found to be low is a helpful positive finding in making a diagnosis of rheumatic heart disease.[14] While there is no unanimity of opinion on the diagnostic value of the vital capacity, our experience would seem to point up the observation that this procedure is most helpful in assessing the functional state of the left heart. Results of cardiac fluoroscopy should be carefully recorded according to standards agreed upon in advance, so as to allow for future comparison (Table 2). Having completed fluoroscopy, the examiner is free to order such laboratory tests as he may feel will help him, i. e., blood cell counts, sedimentation rate, antistreptolysin titers, urinalyses, etc. If the referring doctor has not tested the hemoglobin or urine, these tests may be done. It is well to know exactly any degree of anemia and to be sure that the urine is free from pus. For purposes other than this, we have not found these tests to be of any assistance in making a diagnosis of rheumatic heart disease.

Electrocardiographic abnormalities are found in 95 to 100% of rheumatic children if the tracings are taken at frequent intervals. This would be impracticable in clinic practice. In our clinic, one electrocardiogram, with the possibility of two or three at weekly intervals, is made. It is obvious that the electrocardiogram does not give a diagnosis of rheumatic heart disease, but it can indicate the presence of carditis. If the P-R interval is prolonged, it may be due to rheumatic heart disease, or it may have been prolonged since birth. If it changes on a later tracing, it is a strong point in favor of carditis. Other changes of nonspecific nature may be disturbances of rhythm and alteration in P, QRS, and T waves.[25] The $Q\text{-}T_c$ is measured as noted above. If it is 0.415 or above, one or several more tracings are taken until we assure ourselves as to the child's emotional serenity during the test. If at that time the $Q\text{-}T_c$ is 0.415 or above, the patient has carditis.* In the presence of an abnormal rhythm—i. e., metronomic or tumultuous—a normal or lowered $Q\text{-}T_c$ alerts one to the possibility of pericarditis.

A summary of the areas of inquiry where the physician may make a positive or presumptive diagnosis of rheumatic heart disease is as follows:

Positive Diagnostic Criteria.—1. Rheumatic heart disease in both parents of the patient justifies, in our experience, a diagnosis of potential heart disease in the presence of cardiac findings of questionable significance.

2. The finding by fluoroscopy of an enlarged left auricle and left ventricle in the absence of clear criteria of congenital heart disease predicates the diagnosis of rheumatic heart disease until proved otherwise.

3. A Grade 3 systolic or louder murmur at the apex, transmitted to the left axilla, will prove to be rheumatic heart disease in most children examined in the clinic.

4. Evanescent prolongation in the A-V conduction in the presence of other "rheumatic-like" symptoms is considered evidence of carditis.

5. A prolonged electrical systole ($Q\text{-}T_c$), in our experience, is evidence of the presence of carditis. Failure to find a specific explanation for the carditis leaves rheumatic carditis as the diagnosis of choice.

Presumptive Diagnostic Leads.—1. A positive family history of rheumatic fever and/or rheumatic heart disease in a "sickly" child whose predominant behavior pattern is that of fatigability is presumptive evidence of a mild rheumatic activity in the absence of classic manifestations.

* References 13 and 26-28.

2. Definite changes in heart sounds and murmurs on repeated examination should point to further exploration for the presence of mild carditis.

3. Chloreiform movements or a history of Sydenham's chorea in the presence of minimal cardiac findings should serve as an incentive for further assessment of the heart for the presence of rheumatic heart disease.[29]

4. "Nonspecific" electrocardiographic findings in a child who is otherwise well, particularly, a prolonged A-V conduction, notched P-waves, etc., may be the only presumptive signs of rheumatic heart disease.

5. A generally enlarged heart in a child, in the absence of any definite etiologic diagnosis, may be considered as presumptive evidence of rheumatic heart disease.

Helpful Leads in Diagnosis.—1. The child who is "not well" but is not definitely ill may harbor a mild insidious carditis.

2. An older child who shows a marked depletion of vital capacity in the absence of upper respiratory or pulmonary disease may thus show early left ventricular insufficiency in rheumatic carditis.

3. Progressive pallor out of proportion to the level of the hemoglobin is similar to the almost typical pallor of active rheumatic carditis.

4. Our experience in clinic practice does not warrant an adherence to some of the commonly mentioned laboratory criteria, erythrocyte sedimentation rate, antistreptolysin titer, low grade fever, etc.

In summary, it may be said that the diagnosis of rheumatic heart disease and rheumatic fever in the absence of a classic history and the major and minor manifestations of rheumatic fever has become a clinical problem of major proportions. The diagnostic characteristics of the disease have changed, and there is solid evidence that the natural history of rheumatic fever has eluded clear description. The clinic patient is assessed on the basis of some of the older and more orthodox criteria. This may, in fact, be responsible for the "overdiagnosis" and "underdiagnosis" of these cases. An attempt is made in this communication to classify into three categories the diagnostic criteria evolved in clinic practice. These, we believe, offer a basis upon which a children's cardiac clinic can hope to screen the mildest type of rheumatic fever, the patient with minimal rheumatic heart disease, and to remove the stigma of rheumatic heart disease from the patient who has thus been identified on insufficient evidence. The diagnostic criteria here proposed fall into three categories: (1) positive evidence, (2) presumptive signs, and (3) helpful diagnostic criteria.

SUMMARY

Analysis is made of 306 school children with questionable symptoms of cardiac disease seen in a diagnostic cardiac clinic.

The changing symptomatology of rheumatic disease is commented upon, with illustrative case histories.

A method is suggested for organizing a diagnostic cardiac clinic, with particular emphasis placed on the methods of examining the child, recording the data, and evaluating the picture presented.

Based upon the method of examination outlined, the diagnostic criteria are suggested.

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RADIOACTIVE IODIDE UPTAKE OF NORMAL NEWBORN INFANTS

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THYROID function of the newborn was studied by Danowski and co-workers [1] and by Man and co-workers,[2] who determined the plasma level of the thyroxine-like protein-bound iodine and butanol-extractable iodide. In infants 1 to 3 days old protein-bound iodine averaged 12.0 γ per 100 cc., and butanol-extractable iodine in infants of 2 to 6 days was 7.0 to 11.7 γ per 100 cc. These results are compatible with hyperthyroidism in adults or older children.[2] Several reports * indicated that I^{131} uptakes by the thyroids of normal children "less than 1 year" to 14 years of age were well within the broad range of normal adults, i. e., less than 50% of the injected dose of I^{131} accumulated in the thyroid area after 24 or 48 hours.

Apparently, no I^{131} studies have been reported on newborn infants. The absence of such studies results partly from the previous lack of satisfactory instruments for accurate detection of safe doses, such as 1.0 μc,† of I^{131} in the thyroid.

METHODS

Seven normal newborn boys, 2 and 3 days old and weighing 7 to 9 lb. (3,175 to 4,080 gm.), were studied. Six of the subjects were Negroes, and one, no. 2, was Caucasian. Five of the infants were fed at breast every four hours, and the remaining two were bottle-fed every four hours.

A scintillation counter ‡ was constructed for this investigation. The lead shield around the scintillation crystal extended as a lead tube 5 in. (12.7 cm.) beyond the crystal. The open end of this tube was placed snugly against the objects counted (thyroid area, thigh, injection site, or syringe containing the I^{131} dosage). The background was 110 to 118 counts per minute, and all thyroid counts were 14 to 25 times this background.

The test dose of I^{131} § was drawn into a 0.25-cc. syringe by means of a 27-gauge needle. The syringe needle and solution were then held across the end of the lead tube, and a count of the gamma radiation was recorded. The test dose was injected deeply into the gluteus maximus muscle of the infant, and subsequently the syringe and needle were again counted. The difference

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* References 3-6.

† One microcurie of I^{131} in a thyroid weighing 2.4 gm. will produce a maximum total radiation of 60 r (rep), or 144 gm.-r (grams × roentgen equivalents physical). A gastrointestinal x-ray series with fluoroscopy in an infant results in exposure to at least 20 r, or 3,600 gm.-r. The treatment of thyrotoxicosis in an adult with a 30-gm. thyroid will usually require 5,000 r (rep), or 150,000 gm.-r, from I^{131} given as a single dose.

‡ The scintillation tube was obtained from Nuclear Research Corp., Grays Ferry Ave., Philadelphia. A discriminator and preamplifier was built by B. P. McKay, Research Associate, University of Tennessee.

§ Sterile tracer solution (obtained from Abbott Laboratories, North Chicago), 250 μc of I^{131} per cubic centimeter.

between these two counts was taken as the injected dose,‖ and this was between 1 and 1.5 μc. Twenty-four hours later, the thyroid area of the infant was held against the end of the lead tube, and three counts of one minute each were recorded. The nonthyroidal tissue background was obtained by counting over the thigh. This tissue background was subtracted from the counts per minute of the thyroid area to obtain the I^{131} content of the thyroid gland.¶ Correction was made for 24-hour radioactive decay by dividing the thyroid content by 0.917, and the result was divided by the injected dose in counts per minute, to compute the thyroid uptake as percentage of injected dose.

RESULTS

The results of this study are summarized in the Table. It was evident that in six of the seven infants 60% or more of the I^{131} dosage was taken up and retained in the thyroid area. Two of the subjects, No. 6 and No. 7, accumulated in the thyroid over 90% of the I^{131} test dose. The lowest uptake, in No. 3, was 45.5%, which would be borderline high for an adult.

The Table shows the actual dosage of I^{131} given to each infant and the final counts per minute for the injection site and for the thyroid. The radioactivity of the injection site was found to be the same as the tissue background. This indicated complete absorption of the injected I^{131}.

Results of Study

Patient No.	Age, Days	Inj. Dose, Counts/ Minute	24 Hr. After Injection		
			Inj. Site, Counts/ Minute †	Thyroid *	
				Counts/ Minute	% of Inj. Dose
1	3	3,700	118	2,240	61
2	3	3,680	238	2,300	62
3	3	3,340	78	1,520	46
4	2	2,910	81	1,760	61
5	2	2,840	66	1,920	67
6	2	2,700	67	2,640	97
7	3	2,440	71	2,300	94

* Counts per minute over neck minus counts per minute of tissue background and corrected for 24 hr. decay.
† Corrected for background.

COMMENT

These studies show that the thyroid uptake of iodide is stimulated in the newborn infant. Such data, together with the reports of high protein-bound-iodine levels # in infants of the same age, suggest that the newborn infant may experience a period of physiological hyperthyroidism. This could result from several possible mechanisms, i. e., (*a*) increased sensitivity of the thyroid to thyrotropic hormone, (*b*) increased production of thyrotropic hormone, or (*c*) complex alterations of endocrine balance.

‖ The accuracy of this method for estimating the dose was tested by injecting the solution into a ball of cotton 1 cm. in diameter. The cotton was placed at the end of the lead tube and the I^{131} counted. The actual radioactivity in the cotton was 4% greater than the calculated amount.

¶ The error due to secondary radiation was tested by a water phantom [7] and found to be 11%. This was shown to be counteracted, since the thyroid gland was counted at a greater distance (by 4 to 8 mm.) than the injection dose.

References 1 and 2.

Because several explanations are possible, no therapeutic implications should be drawn from these data until specific experiments have demonstrated the usefulness of possible therapy.

It was necessary to use parenteral injection of the I^{131} tracer dose because valid determinations of the percentage uptake require complete retention of the administered dose. The error which would result from possible regurgitation of gastric contents, common among infants, was thereby eliminated.

The use of radiation in the very young organism is open to some question (Footnote †, p. 439). Therefore, great care and minimal dosage were necessary. The fact that I^{131} has a physical half-life of only eight days means that if there were no metabolic loss of I^{131} the total body radiation would be reduced by 94% in one month by physical decay; after two months a maximum of 0.3% of the original dose could remain in the body. Actually, the metabolic turnover of iodine within the body results in a biological half-life of less than eight days, that is, the effective decay is accelerated by excretion.

The body is always exposed to a certain amount of radiation from atmospheric background and natural-occurring radioactive isotopes. The common form of potassium is radioactive and present in all the body cells. These facts alone may give a false sense of security, because the possible danger of I^{131} results from its great concentration in the cells of the relatively small thyroid gland and from its ionizing beta radiation (in addition to its gamma radiation). No objective biological effect has been reported from a single dose of 100 μc of I^{131} administered to adult human beings.

The dosage used here was calculated on the same weight basis as the 100 μc tracer dose commonly used in adults. The result was divided by four to be well below the per pound adult dose. The infant and adult are not strictly comparable because the rapidly growing infant may be more susceptible to radiation than the mature adult. The dosage was considered by a local group consisting of a radiologist, a radiation physicist, two internists, two pediatricians, a physiologist, and a pathologist. The group considered that according to our best information the dosage of 1 to 2 μc of I^{131} in a 7- to 9-lb. newborn infant was not expected to be harmful. The procedure was described to the mothers of the infants studied, and the mothers gave consent for the study before the tests were made. Only boys were studied because of the low incidence of spontaneous thyroid dysfunction in males. The infants were thoroughly examined and found to be normal before they were studied. The I^{131} was administered by a physician, a film badge was kept within the basinette to obtain a record of the radiation exposure, and disposable diapers were employed during the hospitalization. The children will continue to be evaluated periodically by our outpatient pediatric clinic.

SUMMARY

The I^{131} uptake by the thyroid of seven normal newborn infants has been demonstrated to lie within the range of values which would be found in hyperthyroid adults. The method employed is simple, requires only 1 μc of I^{131}, and it may prove useful in the diagnosis of thyroid abnormalities in infants. A discussion is presented regarding the implications and precautions of the procedure.

Dr. James N. Etteldorf, of the Department of Pediatrics, collaborated in this investigation.

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HONEY IN INFANT FEEDING

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INTRODUCTION

HONEY was extensively used in ancient times as a supplement in infant feeding, particularly with newborn babies.[1] In more modern times it has in large part been displaced as a source of carbohydrate by other sugars except in some countries of the Middle East and Asia, particularly Japan. In these countries, for practical reasons, honey has always enjoyed considerable popularity, and the science of apiculture is highly developed. This is readily understandable, since honey is found free in nature, is easily produced, and requires no treatment or preparation before use. In this country, honey has been used chiefly in rural areas and, even in these areas, only in a sporadic fashion. There were many reasons for this, but among the most important were the lack of uniformity in the product and our inability to produce honey in adequate quantities. In recent years, however, the beekeeping industry has been greatly expanded and, with improved methods of apiculture, is now producing a uniform product, free from contamination, at relatively low cost. A major factor in this revived interest in apiculture has been the investigations of the Department of Agriculture, which have demonstrated that the wild bee was gradually becoming extinct because of deforestation. Since one of the most important functions of the bee is pollinization, our agricultural economy was seriously affected by this development, and the only solution to the problem was the improvement and development of the domesticated bee. This has been accomplished, and, as a concomitant to this, superior and more uniform types of honey are available.

Honey has the following composition: water, 17.20%; sucrose, 0.40%; levulose, 39.10%; glucose, 34.00%, and dextrin, 0.45%.[2] The glucose fraction is quickly and readily absorbed and excreted, while the absorption and excretion of levulose occurs at a much slower rate. The presence of levulose therefore tends to minimize wide fluctuations in blood sugar.[3] Honey also contains appreciable amounts of iron, copper, and manganese.[4] The work of Takagi, in the Department of Pediatrics at the University of Tokyo, indicates that in the experimental animal the minerals are readily available for hematopoietic stimulation.* The evidence as to the presence of vitamins in honey is conflicting, and in all probabilities they are not present in significant amounts.†

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This work was aided by a grant from the Lake Shore Honey Products, of Chicago.

* Takagi, Y.: Personal communication to the authors.

† References 2 and 6.

The effect of honey on the nutrition of infants has been recorded by a number of observers, but either on a limited scale or with inadequate detail.‡ Since pediatricians are constantly in search of methods of feeding which will reduce the incidence of feeding problems, viz., regurgitation, poor weight gain, nonspecific enteritis, etc., in small infants, it was felt that comprehensive and comparative observations on the use of honey and other sugars in infant formulas would be of interest.

PLAN OF STUDY

The clinical material utilized in this study was comprised of infants admitted to the New York Foundling Hospital. This is a multifunctioning institution with a capacity of approximately 240 infants and children under 2 years of age, the majority of whom are under 1 year of age. Admission is contingent primarily on social need rather than organic disease, since the institution is devoted to the care of abandoned, neglected, or dependent infants. It follows, therefore, that while most of the infants are admitted as well, they not infrequently present nutritional and emotional problems of greater or lesser severity. Moreover, it should be pointed out that, since these are institutionalized infants, their weight and growth curves cannot be compared with those of noninstitutionalized children. Comparative interpretations of nutritional data, particularly, are therefore valid only between groups within the institution. During their stay, the infants are given complete pediatric work-ups, which include complete blood cell counts and urinalyses and any other laboratory procedures which seem indicated. They remain in the institution until arrangements can be completed for social disposition. The period in residence varies considerably and may range from a few days to several months, the average being three to four months.

Since most of the infants admitted present social problems, it frequently happens that no data on the past feeding history is immediately available. Accordingly, we begin feedings on a somewhat dilute basis, as one does routinely in hospital nurseries. The initial feeding is a 1:2 evaporated milk-water mixture, with no carbohydrate in the very young infants or with at most 2½% carbohydrate. After a few days or even one week of observations, the milk-water mixture is concentrated and the carbohydrate increased to 5% of the total formula, with a caloric value of 110 Calories per kilogram. During the course of this study, all formulas were initially prepared with 2.5% carbohydrate and gradually altered until the carbohydrate comprised 5% of the total formula by volume.

The infants receive a concentrated multivitamin supplement, and solids are added progressively according to age. At the second month, cereals and fruit are added to the diet, in the third month, vegetables, and in the fourth month, egg yolk and infant meats.

For the purpose of this study, the infants were divided into three groups. Group A received the usual evaporated milk-water mixtures, with the addition of honey § as a carbohydrate. Group B received the same formulas, but with a refined

‡ References 2, 3, and 7-9.

§ The honey used throughout this study is a processed and pasteurized light clover honey, and was supplied by the Lake Shore Honey Products, of Chicago. Dark unprocessed honey apparently has a harsher action than the light processed honey.

sugar (Dextri-Maltose No. 1) as the added carbohydrate. The formulas of the infants in the third group, Group C, were supplemented with Karo. Initially we had intended to use only Karo as a control, but subsequently we decided to compare the honey-fed infants with those fed a more highly refined sugar, such as Dextri-Maltose No. 1. All formulas were isocaloric. The diets of the infants were therefore identical in every respect except for the carbohydrates.

Careful observations were made and recorded on work forms separate and distinct from the hospital records. The latter, of course, could be referred to when needed, although this was seldom necessary. Weight curves were kept weekly on younger infants (under one month) and monthly weight and growth curves on older infants. Increases in formula and additions to the diet were carefully recorded, as well as the number and type of stools, illnesses, treatments, etc. In addition to the admission blood cell counts, monthly red blood cell counts and hemoglobin determinations were performed and repeated more frequently when necessary.

Infants remained under observation until the fourth month of age or until their discharge, whichever came first. Seventy-seven per cent of the infants were observed for one month or more. Observations made on newborn babies, even if their stay was short, were incorporated in the study, since we considered it pertinent to compare acceptability and the gastrointestinal reactions to the three carbohydrates in this young age group. It should be noted that most observations recorded were not based on chronological age but on the length of time in the study. Observations after the fourth month of age were discontinued because it was felt that the total intake of supplementary foods varied considerably between infants, and at this time the amount of carbohydrates in formulas is either reduced or discontinued. Supplementary foods, cereals etc., are begun after the first month but as a rule do not significantly alter nutrition until the third or fourth month of life. Consequently the comparative data in regard to formulae is of more significance in any study of this type in the first two months. For practical reasons (personnel, amount of time available for feedings, etc.) we are inclined to maintain infants on formulas for longer periods than one does when managing infants in private practice.

RESULTS

A total of 387 infants were observed in the course of the study, 183 boys and 204 girls. The following tabulation subdivides these totals in terms of groups and sex:

	Group A	Group B	Group C
Boys	60	53	70
Girls	76	62	66
Totals	136	115	136

There were 10.2% nonwhites in Group A, 16% in Group B, and 15% in Group C. Since only a small percentage of the total cases were nonwhites and since they were about equally divided between the three groups, it was felt that a separate analysis of the findings in these infants was not necessary.

Table 1 illustrates the age distribution of the infants when entering the study and Table 2 the length of time the infants remained under observation. Weight curves for the three groups are illustrated in Chart 1 and represent an average of the weekly weights. Table 3 represents the average weekly weight increments by

TABLE 1.—*Distribution by Ages and Groups at Start*

Ages	Group A	Group B	Group C
0-1 wk.	34	29	38
1-2 wk.	41	19	23
2-3 wk.	11	12	7
3 wk.-1 mo.	7	7	18
1-2 mo.	17	33	23
2-3 mo.	13	12	11
3-4 mo.	9	1	5
4 +	3	1	6
Unknown *	1	1	5
Totals	136	115	136

* Abandoned infants whose exact age was not known; most of these infants, after developmental testing, were given an estimated age of under one month.

TABLE 2.—*Length of Time on Study*

	1 Week	2 Weeks	3 Weeks	4 Weeks	8 Weeks	12 Weeks	16 Weeks
Group A	9	7	4	41	32	21	22
Group B	8	8	5	19	26	13	36
Group C	22	17	10	24	33	18	12
Totals	39	32	19	84	91	52	70

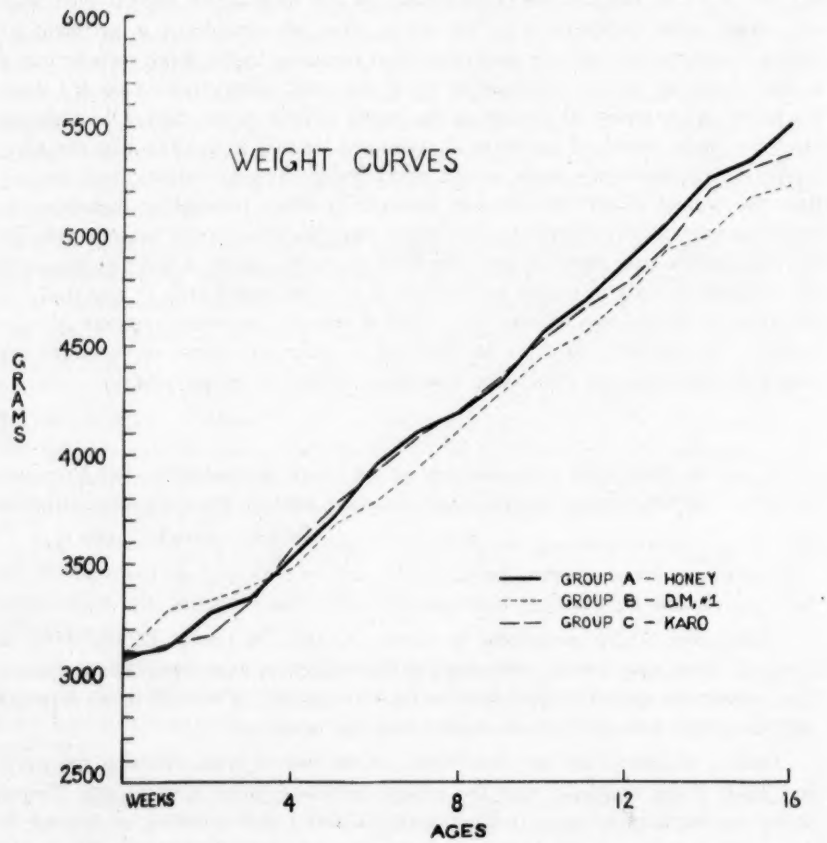

Chart 1

months and the average length increments by months during the period of observation. The former demonstrate very clearly the statement previously made that these infants do not gain weight as well as infants who receive individualized attention in their own homes.

The monthly average of red blood cell counts and hemoglobin (Sahli method) are listed in Table 4.

Chart 2 represents the incidence of nonspecific enteritis occurring in infants after they had been allocated to the three groups. The diagnosis of nonspecific enteritis includes those cases which present no physical findings of infection, but whose stools become semiloose to watery and who also fail to gain adequately. We consider that the consistency of the stools correlated with the weight gives a more objective interpretation than, for example, the type of stool or the frequency of stools alone. It is not unusual for an infant in the first week or two of life

TABLE 3.—*Average Weekly Weight Gains and Average Height Increments*

Observation Period	Average Weekly Weight Gains, Gm.			Average Height Increments, Gm.		
	A	B	C	A	B	C
1 Mo.	176	167	133	5.2	5.2	4.5
2 Mo.	161	181	159	2.5	2.4	2.6
3 Mo.	161	181	161	2.8	2.1	1.1
4 Mo.	161	161	156	1.6	1.6	1.3

TABLE 4.—*Red Blood Cell Count and Hemoglobin Averages*

Observation Period	Red Blood Cell Counts			Hemoglobin		
	A	B	C	A	B	C
Start	4,520	4,270	4,350	14.7	13.5	14.3
1 Mo.	3,822	4,088	3,852	11.0	11.9	10.7
2 Mo.	3,704	3,927	3,626	10.0	12.0	9.8
3 Mo.	4,284	3,927	3,899	10.6	11.3	9.8

to pass occasional semiloose, loose, or even watery stools. By the same token, some infants will have seven or eight stools daily, but of a good consistency. The average number of stools in the first two weeks of life vary from four to six, and after that period from two to four, but there are wide individual differences. Therapy for these cases consisted of either a short starvation period followed by a temporary dilution of formula, discontinuing the carbohydrate, administering a hygroscopic agent, or medication in the form of sulfadiazine or antibiotics. The latter is used empirically, the rationale being that either the intestinal flora is altered or that an inapparent infection is present. Cases of nonspecific enteritis, while generally not of serious import, can be very disturbing and when they occur must be treated. In this connection it is interesting to note that, over a period of time, we have alternated various recommended types of oral treatment for this condition, and we have found that omitting one or two feedings and diluting the formulas for 24 hours is by far the most satisfactory method of handling the problem. Most of the cases in Chart 2 were treated orally. In our experience, 7% of these cases eventually require parenteral support, and there was no appreciable variation from this figure in the current study.

In Table 5 we have listed the incidence of feeding problems under the general term "Nutritional Morbidity." Poor weight gain was in most cases due to inacceptability of the formula offered, but occasionally to prolonged irritability. Irritability of short duration is not an unusual feature in our infants during their first few days in the institution and is frequently due to emotional disturbance. It has many of the features of colic with one outstanding exception: these infants do not gain weight as do colic infants at home who receive individual attention. When this syndrome manifests itself, the nurses and voluntary aides are alerted to the added

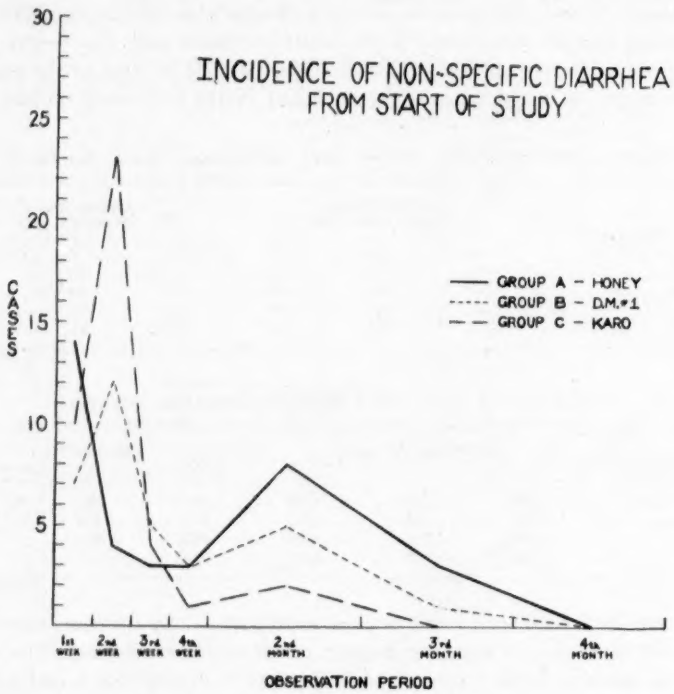

Chart 2

emotional needs of the infant, and formula alterations are made only when the infants fail to respond to this increase in personal attention.

While it is well known that there is an expected drop in hemoglobin and red blood cell counts in the first three months of life and then a spontaneous rise, we have observed that the limit of this depression is rarely under 10.4 gm. (Sahli) in the average case.|| Treatment of these physiological anemias is not undertaken, as pointed out in Table 5, unless the infant fails to thrive.

Table 6 gives the frequency of infection and diaper rashes by diagnosis rather than by case. Since the great majority of these infants remain on an average of four months in the institution, they are liable to repeated attacks of respiratory

|| References 10 and 11.

TABLE 5.—*Nutritional Morbidity*

Observation Period / Groups	1st Wk.			2d Wk.			3d Wk.			4th Wk.			2d Mo.			3d Mo.			4th Mo.			Totals		
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
1. Regurgitation and/or vomiting (without other illness)	2	0	2	0	0	5	0	0	1	0	1	0	0	1	0	1	0	0	0	0	0	3	2	8*
2. Poor weight gain (refusal of adequate intake)	1	0	2	0	1	10	0	1	7	1	1	4	0	0	0	0	0	0	0	0	0	2	3	23†
3. Anemia ‡	0	1	0	0	1	2	1	0	3	0	0	1	1	4	1	0	1	1	0	0	3	2	7	11
4. Eczema	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	1	1	0	1	0	1	3	1

* Formula discontinued in 1 instance because of persistent regurgitation and vomiting.
† Formula discontinued in 14 instances because of failure to accept adequate intake.
‡ Diagnosis entertained only when low hemoglobin was associated with failure to gain and/or to do well.

TABLE 6.—*Morbidity Rates**

Observation Period / Groups	1st Wk.			2d Wk.			3d Wk.			4th Wk.			2d Mo.			3d Mo.			4th Mo.			Totals		
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
1. (*a*) Respiratory infections	9	4	17	15	8	11	9	11	7	21	23	24	13	14	8	14	6	2	2	10	1	83	76	70
(*b*) Respiratory infections plus parenteral diarrhea	2	2	1	0	1	3	2	0	2	0	1	0	1	0	1	0	0	0	0	0	0	5	4	7
2. Diaper rashes	10	6	8	9	6	16	4	2	6	6	10	5	14	4	8	1	2	9	2	2	0	46	32	52

* Incidence by frequency of diagnosis, not by case.

infection and to recurrences of diaper rashes. In reviewing our data, we felt that the frequency with which the diagnosis was made in the various groups was more significant than a case tabulation.

COMMENT

During this study our chief interest was in the nutritional response of the infants to the formulas offered, which differed only in the type of carbohydrate. Therefore our attention was centered upon weight and growth increments, hemoglobin values, incidence of nonspecific enteritis, and feeding problems.

Chart 1 illustrates that there was no statistically significant difference in the over-all weight curves; however, further analysis did demonstrate that in the average weekly weight gains there was a noticeable variation. Table 3 shows that during the first month of observation the average weekly gain for honey-fed infants (Group A) was 176 gm., for the infants who received Dextri-Maltose No. 1 (Group B) it was 167 gm., and for the infants fed Karo (Group C) it was 133 gm. This is almost identical with the average weekly weight gain chronologically, which for infants up to one month of age was for Group A, 179 gm., Group B, 167 gm., and for Group C, 130 gm. It will also be noted in Table 3 that this initial advantage in average weekly weight gain of the honey-fed group was subsequently surpassed by the Dextri-Maltose group, but not by the Karo group. One of the explanations for the poor weight gain of Group C during the first month is apparent in a study of the comparative incidence of nonspecific enteritis between the three groups. The total number of cases did not vary too much; there were 35 cases of nonspecific enteritis in Group A, 33 cases in Group B, and 40 cases in Group C. Chart 2 shows, however, that by far the highest incidence of this condition occurred in Group C infants during the first two weeks after Karo was introduced. It was particularly high in the second week, around the time when the formulas are concentrated and the carbohydrate is raised from 2½ to 5% by volume. Within the first two weeks after the formulas were introduced, honey-fed infants (Group A) had 18 cases of nonspecific enteritis, Dextri-Maltose-fed infants (Group B), 19 cases, and Karo-fed infants (Group C), 33 cases.

Still another explanation for the relatively poor weight gain in the Karo-fed infants is in the incidence of feeding problems other than enteritis. It was never necessary in either the honey or the Dextri-Maltose group to discontinue the formula because of persistent regurgitation, vomiting, failure to gain, or inacceptability, but this was necessary in 15 instances in the Karo-fed infants (Table 5). It was noticed that failure to gain when not due to emotional factors was most frequently due to inacceptability. Most infants responded avidly to honey formulas, and while they responded well to Dextri-Maltose formulas, their enthusiasm for the latter was not as great.

We have taken advantage of this ready acceptability of honey in managing prematures whose weights, despite adequate caloric offerings, have remained stationary for a number of days. This, of course, is not an unusual occurrence with prematures and frequently, with no alteration in formula, they suddenly "take hold" and begin to gain. Honey was added to the formulas of 16 of these infants, and in 6 there was an immediate and sharp increase in the rate of weight gain.

In linear growth also, the honey and Dextri-Maltose groups did better than the Karo infants, and it is probable that the explanation for this is the same as that for the superiority in weight gain previously discussed.

With respect to red blood cell counts and hemoglobin averages, honey was superior to Karo, but not quite as satisfactory as Dextri-Maltose (Table 4). Two of the honey-fed infants required iron therapy for physiological anemia, while seven of the Dextri-Maltose group and 11 of the Karo group were so treated (Table 5). This is probably significant, especially since in the honey group there was a higher incidence of respiratory infections (which tend to induce secondary anemia) than in the other two groups, particularly Group C (Table 6).

The incidence of respiratory infections was somewhat higher in Group A than in the other two groups, while the incidence of diaper rashes was approximately the same in all groups.

SUMMARY AND CONCLUSIONS

A total of 387 infants were divided into three groups (A, B, and C) and offered isocaloric formulas reinforced with honey, Dextri-Maltose No. 1, or Karo. Group A infants received honey-supplemented formulas, Group B formulas were supplemented with Dextri-Maltose No. 1, and Group C formulas contained Karo.

Honey-fed infants were superior to Karo-fed infants in respect to average weekly weight gains, linear growth measures, and hemoglobin values and compared favorably although were not superior to Dextri-Maltose-fed infants. Within the first two weeks after the formulas were introduced, 18 honey-fed infants and 19 Dextri-Maltose-fed infants developed nonspecific gastroenteritis. During a comparable period of time, 33 Karo-fed infants developed this condition. Feeding problems severe enough to cause discontinuation of the formula did not occur in the honey or Dextri-Maltose groups, but occurred in 15 instances in the Karo group. Two cases of physiological anemia requiring therapy occurred in the honey-fed group, seven in the Dextri-Maltose group, and 11 in the Karo group.

It would seem from the observations in this study that honey has a definite place in infant feeding.

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SIGNPOSTS ON THE HIGHWAY OF GROWTH

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FOR MORE than a score of years I have been engaged in instructing medical students, interns, and pediatric residents in some of the fundamental aspects of the growth and development of children. Whereas it is true that average or median figures for height and weight and appraisal of the person in terms of percentage deviation therefrom can best be determined by reference to published tables or charts, it is nevertheless desirable that the student (or embryonic pediatrician) be able to formulate mentally without reference to tables a rough assessment of the nutritional and developmental status of the individual patient. Over the years I have therefore presented to my students a series of "aids to memory" to encourage quick and approximate assessment of the developmental status. The mnemonics have been of such type as the following: "at 3 years the child is 3 ft. tall"; "at 4 years the child is 40 in. tall"; "at 7 years the weight of the child in pounds is seven times the weight at birth," etc. The mnemonics have been presented to students in tabular form on a blackboard under the title "Signposts on the Highway of Growth." As the years have gone by and with the publication of new standards of what is normal or average, it has become apparent either that children of a new generation are larger than their parents or that earlier standards for normal were based on measurements of a sub-optimal group.

The 12th addition of the Holt-McIntosh textbook,[1] published in the spring of 1953, presents figures for average growth in height and weight which in general are greater than those published in the 5th edition (1950) of the Mitchell-Nelson textbook.[2] Normative figures in the Holt-McIntosh book were taken from the data of Simmons.[3] Data in the Mitchell-Nelson book were gleaned from two sources: from birth to 5 years from figures assembled at the Harvard School of Public Health,* and from 5 to 18 years from studies at the Iowa Child Welfare Research Station.[4] The textbooks are recent editions—too recent, indeed, to warrant the conclusion that 1953 children are significantly taller and heavier than 1950 children. The data have nevertheless compelled a revision of teaching material in the mnemonics "Signposts on the Highway of Growth." In the belief that others may find the aids to memory to be useful, they are being published.

From the Children's Hospital Research Foundation and the Department of Pediatrics of the University of Cincinnati College of Medicine.

* Stuart, H. C., and Stevenson, S. S.: Care and Evaluation of Well Children, in Nelson.[2]

I. WEIGHT AS A FUNCTION OF AGE

Current signposts deal first with body weight at progressing ages. Average weight at birth should be memorized. Standard figures vary from 7.1 lb. for girls, given by Holt-McIntosh, to 7.5 lb. for boys, presented by Mitchell-Nelson. The average for boys and girls of data in the two books is 7.35 lb., or 7 lb. 6 oz.

From the ages of 3 months to 12 months, average body weight may be approximated from a single formula, namely, weight in pounds equals age in months plus 11, or W (pounds) = A (months) + 11. In terms of figures published in the two textbooks, the accuracy of prediction by the formula is shown in Table 1. In each illustrated instance the predicted weight lies within the range given by both books for both sexes. On the average, somewhat greater accuracy of prediction would result if the constant in the equation were changed from 11.0 to 10.7. Since the purpose of the equations is to make them easy to memorize, the slightly increased accuracy scarcely justifies abandoning the round figure.

The student may next take note of a simple aid to memory: "At 30 months of age (2½ years) the average child weighs 30 lb." The published figures show for

TABLE 1.—*Weight Prediction from Age (Three to Twelve Months)*

	Weight, Lb.					
	Mitchell-Nelson		Holt-McIntosh		Grand Average	Predicted by Formula
Age, Mo.	Boys	Girls	Boys	Girls		
3	12.6	12.4	14.3	13.0	13.1	14
6	16.7	16.0	18.7	17.0	17.1	17
9	20.0	19.2	21.7	19.7	20.2	20
12	22.2	21.5	23.8	21.9	22.4	23

Mitchell-Nelson, boys, 30 lb., girls 29.6 lb.; for Holt-McIntosh, boys, 31.5 lb., girls 30.1 lb. The grand average is 30.3 lb.

The student will next be helped by another approximation: "at 3.5 years the average child weighs 35 lb." Mitchell-Nelson gives an average at this age for boys of 34.3 lb. and for girls of 33.9 lb. Holt-McIntosh gives an average for boys of 35.9 lb. and for girls of 35.0 lb. The grand average for both books is 34.8 lb.

The foregoing mnemonics will enable the student to formulate mentally a close approximation of average body weight at any age from birth to 3½ years. Because the formula, W (pounds) = A (months) + 11, overestimates the weight at 3 months of age, there is justification for purposes of interpolation for assuming that weight at 1 month will equal the birth weight. Weight at 2 months of age can therefore be approximated as the average of birth weight and weight at 3 months, namely, as 10.7 lb. or 10 lb. 6 oz. Similarly, estimated weight between the ages of 12 months (1 year) and 30 months (2½ years) can be approximated satisfactorily by linear interpolation (Table 2).

After the age of 3½ years, the slope of the growth curve increases so slowly as to permit the assumption of a linear relationship between age and weight over two subsequent four-year periods. From the ages of 4 to 8 years inclusive, average body weight in pounds approximately equals six times the age in years plus 12. From ages 8 to 12 years, inclusive, average body weight in pounds approximately equals seven times the age in years plus five. Both formulas, being inclusive, cover the

weight at 8 years. For this age the former formula, 6A + 12, yields an estimated average weight of 60 lb. and the latter formula, 7A + 5, an estimated weight of 61 lb. The average of figures given in the two texts for both sexes is 60.3 lb. Table 3 presents the accuracy of prediction by the formulas over the age range from 4 to 14

TABLE 2.—*Weight Prediction from Age (Twelve to Thirty Months) by Linear Interpolation Between Formula Data at Ages Twelve and Thirty Months*

	Weight, Lb.					
	Mitchell-Nelson		Holt-McIntosh			
Age, Mo.	Boys	Girls	Boys	Girls	Grand Average	Predicted by Interpolation
12	22.2	21.5	23.8	21.9	22.4	23.0
18	25.2	24.5	26.9	25.0	25.4	25.3
24	27.7	27.1	29.2	27.6	27.9	27.7
30	30.0	29.6	31.5	30.1	30.3	30.0

TABLE 3.—*Weight in Pounds as a Function of Age*

	Weight, Lb.						
	Average (or Median) Values from Standard Texts					Predicted by Formula	
	Mitchell-Nelson		Holt-McIntosh				
Age, Yr.	Boys	Girls	Boys	Girls	Grand Average	6A (Yr.) + 12	7A (Yr.) + 5
4	36.4	36.2	38.1	37.2	37.0	36	..
5	40.5 *	40.5 *	....	....	....	..	..
5	42.8 †	41.4 †	42.8	42.3	41.9	42	..
6	48.3	46.5	48.2	48.3	47.8	48	..
7	54.1	52.2	54.2	54.5	53.8	54	..
8	60.1	58.1	61.0	61.9	60.3	60	61
9	66.0	63.8	68.4	69.6	67.0	..	68
10	71.9	70.3	76.8	78.1	74.3	..	75
11	77.6	78.8	85.6	88.4	82.6	..	82
12	84.4	87.6	95.2	100.4	91.9	..	89
13	93.0	99.1	105.7	110.5	102.1	..	96
14	107.6	108.4	119.1	120.1	113.8	..	103

* Harvard data (Stuart, H. C., and Stevenson, S. S.: Care and Evaluation of Well Children, in Nelson [3]).
† Iowa data.[4]

TABLE 4.—*Average Growth in Weight for Girls and Boys (Mitchell-Nelson and Holt-McIntosh)*

Age	Weight, Lb.	Age	Weight, Lb.
Birth	7.35	3.5 yr	35
3-12 mo	A (mo.) + 11	4- 8 yr	6A (yr.) + 12
30 mo	30	8-12 yr	7A (yr.) + 5

years. It is clear that after the age of 12 years the formulas no longer yield accurate predictions.

The foregoing mnemonics and formulas predicting weight from age are summarized in Table 4.

II. HEIGHT AS A FUNCTION OF AGE

Signposts have also dealt with the relationship between age and height (or length). The items to be memorized are much simpler than those relating age to weight. Average figures for both sexes show that body length at birth approximates 20 in. By the age of one year the average figure has increased to 30 in. These

are round figures and not too hard to remember. Although it is difficult for the deviser to abandon such memory gems as those cited in the first paragraph of this paper or another which states that "at 7 years the height equals 7 times 7 in.," the linear relationship between height and age after the age of 2 years is so close that the mnemonics are not really needed. From the age of 2 years to 14 years, height can be approximated by a formula which states that the height in inches equals two and one-half times the age in years plus 30. In algebraic form the formula reads H (inches) = 2½A (years) + 30. Table 5 illustrates the accuracy of prediction by the formula.

III. WEIGHT AS A FUNCTION OF HEIGHT

With respect to developmental status, it is well known that the correlation between height and weight is higher than that between age and weight or age and

TABLE 5.—*Height in Inches as a Function of Age*

	Height, In.					
	Average (or Median) Values from Standard Texts					
	Mitchell-Nelson		Holt-McIntosh			
Age, Yr.	Boys	Girls	Boys	Girls	Grand Average	Predicted by Formula (2½A [Yr.] + 30)
2	34.4	34.1	34.4	33.9	34.2	35.0
3	37.9	37.7	38.0	37.6	37.8	37.5
4	39.7	40.6	40.9	40.7	40.5	40.0
5	42.8 *	42.9 *	....	....	....	....
5	43.8 †	43.2 †	43.6	43.5	43.4	42.5
6	46.3	45.6	46.3	46.3	46.1	45.0
7	48.9	48.1	48.7	48.7	48.6	47.5
8	51.2	50.4	51.1	51.1	51.0	50.0
9	53.3	52.3	53.3	53.3	53.1	52.5
10	55.2	54.6	55.2	55.5	55.1	55.0
11	56.8	57.0	57.4	58.1	57.3	57.5
12	58.9	59.8	59.6	60.7	59.8	60.0
13	61.0	61.8	62.0	62.8	61.9	62.5
14	64.0	62.8	64.9	64.1	64.0	65.0

* Harvard data (Stuart, H. C., and Stevenson, S. S.: Care and Evaluation of Well Children, in Nelson [3]).
† Iowa data.[4]

height. Although the formulas of the preceding sections enable approximations of weight and height at different age levels, the approximations are not so good as would have resulted from the elimination of age as a variable. For this reason a direct relationship, independent of age, has been sought between height and weight. The search has led to an approximate formula relating height to weight. At first inspection the formula appears complicated and cumbersome; brief practice in its application will demonstrate that the numerical quantities involved in the computations are invariably small numbers and can sometimes be made mentally without recourse to the scratch pad. The formula is as follows:

$$W \text{ (pounds)} = \left(\frac{H \text{ [inches]}}{2} - 23\right)\left(\frac{H \text{ [inches]}}{10}\right) + 48$$

The formula permits an accurate prediction of average weight from average height during the period from 2 to 12 years. After the age of 12 years the formula underestimates the weight to be expected at any body height. Accuracy of prediction between the ages of 2 and 14 years is shown in Table 6. A couple of illustrations

will clarify the steps involved in computing a prediction. For a child who is 50 in. tall one first observes that half of this figure minus 23 equals 2; one then notes that one tenth of the height equals 5. The product of $\left(\frac{H}{2} - 23\right)$ and $\frac{H}{10}$, therefore, equals 10. Summation of 48 and 10 leads to an estimated weight of 58 lb. For a younger child who is 40 in. tall one notes that half of this figure is 20 and that 20 — 23 equals —3; one-tenth of the height equals 4.0, and the product in the equation is —12.0. Therefore, expected weight at a height of 40 in. is 48 — 12, or 36 lb.

The equation can be solved to show that weight in pounds and height in inches will be represented by indentical figures when the pound-inch level is 44.4. On the average, this level is attained at approximately 5½ years. In general, for children younger than 5½ years the first term of the equation will have a negative value to

TABLE 6.—*Weight in Pounds as a Function of Height in Inches*

Age, Yr.	Grand Average for Boys and Girls Mitchell-Nelson; Holt-McIntosh		Predicted by Formula,* Lb.
	Height, In.	Weight, Lb.	
2	34.2	27.9	27.8
3	37.8	32.5	32.5
4	40.5	37.0	36.9
5	43.5	41.9	42.6
6	46.1	47.8	48.2
7	48.6	53.8	54.3
8	51.0	60.3	60.8
9	53.1	67.0	66.9
10	55.1	74.3	73.1
11	57.3	82.6	80.4
12	59.8	91.9	89.3
13	61.9	102.1	97.2
14	64.0	113.8	105.6

* $W = 48 + \left(\frac{H}{2} - 23\right)\frac{H}{10}$; W = weight in pounds and H = height in inches.

be subtracted from the basic figure of 48. For children older than 5½ years the first term will be positive and added to 48. This circumstance operates to eliminate large numbers in the calculations and so simplifies the arithmetic.

IV. HEAD CIRCUMFERENCE AS A FUNCTION OF AGE

During infancy and early childhood the occipitofrontal circumference of the head is a measure commonly used in assessing the significance of such deviations from the normal average as occur in hydrocephalus, subdural hematoma, cerebral agenesis, etc. Even more than for the relationships among age, weight, and height, the student who seeks to evaluate the significance of the circumference of the head should feel constrained to consult a table of reference. Nevertheless, a few aids to memory can be useful for bedside approximations.

The rate of growth of the head decelerates steadily from birth to maturity. There is no adolescent spurt. The dependence of head circumference on age can be expressed by an exponential equation, too complicated for ready usefulness. Memory must therefore rely on a few orienting mnemonics.

Circumference at birth must be memorized. The average for both sexes in the data of Vickers and Stuart [5] is 13.8 in. It will probably help very little to observe

that this figure equals one-half of the sum of the weight in pounds and the length in inches. Two simple mnemonics cover the period of early rapid growth: "At 7 months the head measures 17 in."; "at 19 months the head measures 19 in." These figures cover the ages where a rough-and-ready assessment of average head circumference is most frequently useful. To be complete, we may note that the round figure of 20 in. is reached at 5 years and that the circumference at 12 years reverses the digits of the age and equals 21 in.

SUMMARY

A collection of "aids to memory" is presented with the objective of simplifying rough approximations of developmental and nutritional status during childhood.

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AMINO-ACIDURIA IN GALACTOSEMIA

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GALACTOSEMIA,* which is frequently familial, is manifested by vomiting, diarrhea, poor weight gain, malnutrition, and the presence of albumin and galactose in the urine while lactose is present in the diet. Jaundice, mental retardation, and cataracts commonly occur. The diagnosis can be made by identification of the sugar in the urine and by a markedly elevated galactose tolerance test with a glucose tolerance test which is within normal limits. Most of these findings are reversible when lactose or galactose is withheld from the diet.

By the use of paper partition chromatography techniques for amino acids, Holzel [19] and Bickel [20] have recently described an increase of the amino acids in the urine of infants with galactosemia. The present paper will describe amino acid studies performed on two children with the disease and discuss the probable mechanism responsible for this amino-aciduria in galactosemia.

REPORT OF CASES

CASE 1.—David P., a white boy, was first seen at the Beth Israel Hospital at 23 months of age. Past history revealed that he was the product of a normal full-term pregnancy and delivery and weighed 6 lb. 2 oz. (2,780 gm.) at birth. On the second day of life, he was started on a standard milk formula and did quite poorly, with loose stools, vomiting, and poor weight gain. Jaundice developed on the sixth day of life. Laboratory studies showed the urine to contain 3+ albumin and 4+ reducing substance. The thymol turbidity was 5.0, icterus index 50, and total bilirubin 8.8 mg. per 100 cc. Because of feeding difficulties, the infant was started on Nutramigen (a hypoallergenic formula) empirically and began to gain weight and appeared to improve. He was, therefore, kept on a milk-free diet for the next 22 months and did very satisfactorily. The diagnosis of galactosemia was considered only after his sibling was found to have the disease.

Physical examination on admission to the hospital at 23 months of age showed a healthy, well-developed, and well-nourished white boy with no abnormal findings. The liver and spleen were not palpable, and no cataracts were seen.

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* References 1-19.

Laboratory studies showed the urine to be free of albumin and reducing substance. The glucose tolerance test was normal. The galactose tolerance tests are summarized in Table 1. Liver function tests showed thymol turbidity 0.8, thymol flocculation 0, cephalin-cholesterol flocculation 0, one-minute bilirubin 0.16 mg. per 100 cc., and total serum bilirubin 0.36 mg. per 100 cc. Sulfobromophthalein (Bromsulphalein) excretion test showed 2.5% retention at the end of 45 minutes, a 5 mg. per kilogram of body weight test dose being used.

Fifty grams of *d*-galactose† was added to the patient's diet daily for 10 days. Clinically, he suffered no ill effects. Liver function tests at the end of the 10 days showed thymol turbidity 1.0, thymol flocculation 1+, cephalin-cholesterol flocculation 2+, one-minute bilirubin 0.15 mg. per 100 cc., total serum bilirubin 0.40 mg. per 100 cc. A sulfobromophthalein excretion test showed 24.8% retention at the end of 45 minutes.

The liver function tests were repeated again 10 days after galactose was discontinued. They showed thymol turbidity 1.0, thymol flocculation 0, cephalin-cholesterol flocculation 0, one-minute bilirubin 0.15 mg. per 100 cc., total serum bilirubin 0.37 mg. per 100 cc.

At the present time, the patient is 3½ years old and normal in every way.

TABLE 1.—*Galactose Tolerance Tests* *

	Case 1	Case 2
Oral Galactose Tolerance Test		
Fasting total sugar	95	102
Nonfermentable sugar	1	9
½ hr. total sugar	276	148
Nonfermentable sugar	138	67
1 hr. total sugar	276	209
Nonfermentable sugar	168	92
1½ hr. total sugar	276	190
Nonfermentable sugar	168	92
2 hr. total sugar	280	168
Nonfermentable sugar	179	92
Intravenous Galactose Tolerance Test		
Fasting total sugar	95	87
Nonfermentable sugar	3	10
15 min. total sugar	190	260
Nonfermentable sugar	94	132
45 min. total sugar	180	254
Nonfermentable sugar	94	153
75 min. total sugar	170	234
Nonfermentable sugar	87	107

* The oral galactose tolerance test was performed with use of a 1.75 gm. per kilogram of body weight test dose. The intravenous galactose tolerance test was performed with use of a 1.2 gm. per kilogram test dose. The fermentable and nonfermentable portions of the blood sugars were determined by the Somogyi method.[21]

CASE 2.—Dana P., brother of David P., was first seen at the Beth Israel Hospital at 2 months of age. Past history revealed that the infant was the product of a full-term normal pregnancy and delivery and weighed 6 lb. 11 oz. (3,030 gm.) at birth. The infant was started on a standard milk formula on the second day of life. On the 10th day, he became jaundiced, had soft frequent stools, vomited occasionally, and gained weight poorly. Laboratory studies revealed albumin and a reducing substance in the urine. The latter was identified as galactose by the osazone and mucic acid technique. Because of this, he was started on Nutramigen and admitted for study.

Physical examination on admission at 2 months of age showed a well-nourished and well-developed white boy with no abnormal findings. The liver and spleen were not palpable, and no cataracts were seen. There was no icterus.

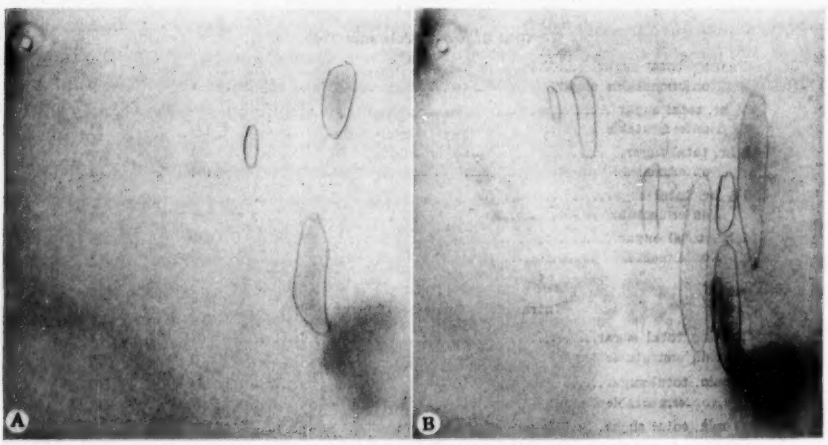
† Manufactured by Difco Laboratories, Detroit.

Laboratory studies showed the urine to be free of albumin and reducing substance. The glucose tolerance test was normal. The galactose tolerance tests are summarized in Table 1. Initial liver function tests showed thymol turbidity 0.2, thymol flocculation 0, cephalin-cholesterol flocculation 0, and one-minute and total serum bilirubin levels normal. Sulfobromophthalein test showed 9.7% retention at the end of 45 minutes.

Fifty grams of *d*-galactose was added to the diet daily for 10 days. On the fourth day, the patient started to vomit feedings. His weight fell from 9 lb. 10 oz. (4,370 gm.) to 9 lb. 4 oz. (4,200 gm.) by the fifth day. He had diarrhea, and the stools became foul-smelling. Liver function tests on the 10th day showed thymol turbidity 1.5, thymol flocculation 1+, cephalin-cholesterol flocculation 3+ and normal bilirubin levels. The sulfobromophthalein excretion test showed 16.7% retention at the end of 45 minutes.

All of the symptoms disappeared when galactose was removed from the diet. Ten days after the galactose was stopped, repeated liver function tests showed thymol turbidity 0.8, thymol flocculation 0, cephalin-cholesterol flocculation 0, one-minute bilirubin 0.13 mg. per 100 cc., and total serum bilirubin 0.25 mg. per 100 cc.

At the present time, the child is 2 years old and normal in every way.



Two-dimensional paper partition chromatography patterns for amino acids. *A*, while the patient was on a galactose-free diet, Case 1. Amino acids present include the following: aminoacetic acid 2+, serine 2+, histidine 3+, and alanine 1+. The amino acids are graded as follows: 5+, marked excess; 4+, very prominent; 3+, prominent; 2+, moderate; 1+, slight but definitely present; ±, trace. *B*, while the patient was taking 50 gm. of added galactose daily. Amino acids present include the following: aminoacetic acid 3+, serine 3+, histidine 3+, lysine 3+, glutamine 2+, tyrosine 1+, tryptophan 2+, methionine ±, and threonine 2+.

AMINO ACID STUDIES

Serum and urine amino nitrogen studies were determined in duplicate on the children on three separate occasions: (1) while on a galactose-free diet, (2) after 50 gm. of *d*-galactose had been added to the diet for 10 days, and (3) after galactose had been discontinued for 10 days. Similar studies were obtained on the parents of these children on two separate occasions: (1) while on a normal diet without added galactose, and (2) after 75 gm. of *d*-galactose had been added to the diet daily for 10 days.

The urine alpha amino nitrogen was based on 24-hour collections and determined by both the gasometric ninhydrin-CO_2 method described by Van Slyke,

MacFadyen, and Hamilton [22] and the copper method of Albanese and Irby.[23] The latter method has the advantage of simplicity, but gives only an approximate value. The results are listed in Table 2. While they were on a galactose-free diet, the excretion of the children with galactosemia was similar to that of normal children of the same weight.‡ The excretion showed a twofold to threefold increase after galactose had been added to the diet for 10 days in both children. This returned to normal again after galactose had been discontinued for 10 days. The parent showed normal excretion of alpha amino nitrogen as compared with adult controls.§ This was true both while they were on a normal diet and after *d*-galactose had been added to the diet for 10 days.

TABLE 2.—*Urine Alpha Amino Nitrogen,* as Determined by Both the Van Slyke and the Copper Method*

	Van Slyke Method				Copper Method			
	Case 1 †	Case 2 ‡	Father	Mother	Case 1 †	Case 2 ‡	Father	Mother
On regular diet	....	....	88.3	72.8	..	..	322	295
On galactose-free diet	22.3	7.8	....	....	66	28	...	...
After galactose added for 10 days	71.5	15.5	67.2	116.6	162	88	245	352
After galactose discontinued for 10 days	28.4	5.8	....	....	97	17	...	...

* Expressed as milligrams per 100 cc. per 24 hours.
† Weight 30 lb. (13,610 gm.).
‡ Weight 10 lb. (4,540 gm.).

TABLE 3.—*Serum Alpha Amino Nitrogen**

	Case 1	Case 2	Father	Mother
On regular diet	...	...	5.1†	4.5†
On galactose-free diet	6.2	5.8	...	...
After added galactose for 10 days	5.7	6.1	5.6	5.5

* Expressed as milligrams per 100 cc.
† Based on plasma, which give slightly lower values.

The amino acids in the urine were further analyzed by the two-dimensional paper partition chromatography technique using phenol and butanol-acetic acid as solvents, as described by Consden, Gordan, and Martin [25] and modified by Dent ‖ (Figure). The amino-aciduria appeared to be generalized, with no one single amino acid being excessively prominent. Several of the essential amino acids were excreted in significant quantities, an excretion which is unusual in normal children.¶ The parents showed chromatographic patterns usually seen in normal adults.

The serum alpha amino nitrogen was determined by the gasometric ninhydrin-CO_2 method described by Hamilton and Van Slyke.[28] The results are listed in Table 3. It can be seen that the levels were normal while the children were on a

‡ References 23 and 24.

§ References 22 and 23.

‖ References 26 and 27.

¶ Hsia, D. Y.: Unpublished data.

galactose-free diet and remained unchanged after they were given added galactose and were showing increased amino acid excretion in the urine. The parents also showed normal alpha amino nitrogen levels in the serum.

COMMENT

Amino-aciduria can occur in at least three different ways: 1. Elevation of amino acid levels in the plasma or serum, which results in a slight "overflow" of those amino acids through the kidney into the urine. This mechanism appears to operate in such conditions as phenylketonuria,# progressive muscular dystrophy,[31] and idiopathic hypoproteinemia.[32] 2. A congenital abnormality of the renal tubules resulting in defective reabsorption of one or more amino acids. Most examples of this defect, such as rickets,[33] cystinuria,[34] and the de Toni-Fanconi syndrome,* have a genetic background and appear to be permanent and irreversible. Recently, a defect in the distal tubule has been demonstrated morphologically in the last of these conditions.[36] 3. A temporary inability of reabsorption of amino acids as a result of the action of poisons on the renal tubules. This has been described in association with lead,[37] uranium,[38] nitrobenzene,[39] and saponated cresol solution (Lysol) [40] poisoning and with Wilson's disease.[41]

The normal alpha amino nitrogen levels in the serum together with the reversibility of the amino-aciduria following the removal of galactose from the diet makes it appear that the first and second of these mechanisms do not play a significant role in galactosemia. Rather, it would seem that galactose has some direct effect upon the renal tubules which permits the alpha amino nitrogen to be excreted in excess and prevents their resorption in the normal manner. Craig and Maddock [42] fed normal young rats a 70% galactose diet with an adequate protein and salt intake and found that such animals excrete a high proportion of their ingested protein nitrogen as peptides and amino acids in the urine as compared with that excreted by the control-fed rats. They attributed this increased urinary nitrogen excretion in part to the increased metabolic demand on the available nitrogen for gluconeogenesis and in part in a competitive inhibition of amino acids and peptides by the renal tubules. Patterson [43] has reported on these observations with regard to glucose.

Various authors † have demonstrated liver damage in association with galactosemia. Mason and Turner [4] have postulated that the low blood glucose levels in these patients result in a relative starvation of all tissues and eventual impairment of function of all of the cells in the body, including those of the liver. Bruck and Rapoport [7] and Mellinkoff [6] have pointed out, however, that hypoglycemia from other causes, such as von Gierke's disease or hyperinsulinism, does not result in similar symptoms or in hepatic or renal damage. They suggest, therefore, that the severe manifestations of this disease are toxic in nature and result from high blood galactose levels. Regardless of the mechanism, the rapid alteration of liver function tests from negative to positive after the addition of galactose to the diet for only 10 days suggests that galactose has a rapid and direct effect on the liver. However,

References 29 and 30.

* References 26 and 35.

† References 12, 14-16, and 18.

the amino-aciduria appears in no way related to this change in liver function. Rather, one conceives of the liver damage occurring over a long period of time because of (1) the chronic toxic action of elevated circulating galactose, or (2) the chronic loss of amino acids through the urine, which, in turn, will cause chronic liver damage and cirrhosis. This same mechanism is believed to operate in Wilson's disease and the de Toni-Fanconi syndrome.

Uzman and Hood [44] have demonstrated amino-aciduria in four asymptomatic siblings of patients with known Wilson's disease. The mother of these children, however, was unaffected. Although amino acid studies have not been done on unaffected siblings of children with galactosemia, the parents of two such children appear to be unaffected.

SUMMARY

Amino-aciduria was demonstrated when galactose was added to the diet of two children with galactosemia. This was confirmed both by quantitative measurements and by paper partition chromatography techniques.

The amino-aciduria was generalized and involved several different amino acids.

It appeared to be primarily renal and probably toxic in nature. Increased protein catabolism in the body as well as saturation of the renal threshold by galactose might be responsible for the loss of amino acids. It appears unrelated to the action of galactose on the liver.

The alpha amino nitrogen metabolism of the parents of these children was completely normal.

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HYDROCEPHALUS CONSEQUENT TO CRANIUM BIFIDUM

Report of a Case Suggesting a New Hypothesis as to One Possible Cause

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THE PROBLEM of cranium bifidum is not nearly so well described in the literature as that of spina bifida, principally because the occurrence of the former is so much rarer than that of the latter. However, Ingraham and Swan [1] were able to amass 84 cases and other reports which indicate that cranium bifidum in its own right is not an inconsiderable problem. The occurrence of hydrocephalus associated with these cranial defects is generally thought to be high. Bucy [2] states that these cranial malformations are frequently associated with hydrocephalus. On the other hand, Ingraham and Swan mention only 4 instances of increasing hydrocephalus in 35 cases with operation. On the whole, however, general medical opinion agrees with Bucy that the incidence of this complication is high.

The cause of hydrocephalus in the case of spina bifida has long been recognized in the Arnold-Chiari complex. The mechanism of the same complication in cranium bifidum, however, is not so obvious. Congenital atresia of the aqueduct, failure of formation of the foramina of Luschka and Magendie, and other associated abnormalities have been offered as explanations. These, however, are exceedingly rare. In his list of associated congenital anomalies, Ingraham mentions only 26 of the cerebellum and brain stem, including 20 cases of Arnold-Chiari malformation. This would leave only 6 cases out of a total of 570 which might have been instances of stenosis of the aqueduct or failure of passageways to form. Recently a case was encountered which may throw some light on one mechanism responsible for a progressively enlarging head.

REPORT OF CASES

CASE 1.—L. B. was first seen at 2 days of age because of a large irregular protrusion in the midfrontal region. This mass was some 5 cm. in diameter; a good portion of it was reddish without any skin over it, and it exuded a straw-colored fluid. Beneath this mass a cranial defect could be felt which was 2 to 3 cm. in diameter. The eyes were set wide apart, and the head measured 34.5 cm. in circumference. The child was operated upon almost immediately in order to forestall meningitis. A cystic mass was removed which was attached to and entered the skull by a circular hard fibrous stalk about 1 cm. in diameter. The mass was demonstrated by x-ray (Figs. 1 and 2).

The baby recovered from the operation satisfactorily, but by 3 months of age the head circumference was 40.5 cm., and hydrocephalus was suspected. By 5 months of age, the head measured 48 cm. in circumference, and, while the baby appeared to be mentally bright and alert, it was noted that his head was strangely shaped, and the frontal areas appeared to be assuming an undue prominence. By the time the child was 2 years of age, the circumference of the head was 51 cm. The examiner thought at that time that he was quite hydrocephalic, particularly in the anterior part of the head, but it was said that there was also a bulging in

Fig. 1.—Location of cystic mass in Case 1.

Fig. 2.—X-ray showing cystic mass attached to and entering the skull.

the region of the posterior fossa. He had a marked degree of hypertelorism. There was a large pulsating cranial defect between and just above the eyes; this area was moderately tense. He also had some scalp veins which were unduly prominent.

Because of the increasing size of the head and other signs of possible hydrocephalus, the patient was hospitalized, and ventriculography was done. This was reported as revealing normal-sized ventricles with no dilatation, deformity, or displacement. A moderate amount of air was noticed on the surface of the brain on the brow-up and brow-down positions. There was abnormality in the contour of the skull, with a very large prominent brow. The sutures appeared normal.

Because of the unusual distance between the anterior horns of the lateral ventricles and the frontal bone, it was hypothesized that this child might have an internal extension of the meningocele originally repaired; therefore, craniotomy was undertaken. To the surprise of the surgeon, no such intracranial meningocele was encountered. Instead, a tumor was discovered between the two hemispheres, directly beneath the original skull defect and attached to the intracranial end of the fibrous band found at the first operation. This tumor was quite vascular and at least the size of an egg. It could be shelled off the medial surface of the right hemisphere, but it appeared to invade on the left to some extent. It was removed *in toto*. The pathological diagnosis was hemangioma. After the operation, all signs of intracranial tension disappeared, and in one month the skull circumference had decreased to 50 cm.

It is well known that spina bifida is frequently associated with intraspinal fibroma and occasionally with teratoma. These tumors give increasing neurological signs which present in the spine. The question arose, therefore, whether hemangioma might be a complication of cranium bifidum. It is an established fact that lesions found in the occipital region are more frequently associated with hydrocephalus and that this is a favorite site for hemangiomas. Our cases were reviewed to see whether we could find any possible instances of patients who could be suspected of having hemangiomas and who progressed to hydrocephalus.

Case 2.—V. T. had a moderate-sized occipital encephalocele which was operated upon when the child was approximately 3 months old. The cerebellar hemispheres protruded into the cranial defect, and there were several nodules of amorphus yellow tissue which were sent to the laboratory for analysis. The cranial cavity was not explored, and the defect was repaired at the cranial level.

The microscopic pathological report stated, "There are areas in which there appears to be hemangioma formation consisting of numerous capillary passages."

After operation, a ventriculogram was made, in which the ventricles appeared to be completely normal in size and position, including the fourth ventricle. Craniolacunia was present. The child progressed to apparent hydrocephalus with a progressively enlarging head and mental retardation.

Case 3.—E. K. W. was even more suggestive of having a possible hemangiomatous malformation. He was a newborn infant with a large occipital encephalocele arising from a stalk measuring approximately 10 cm. in diameter and distending to a mass some 20 cm. in diameter, it being translucent and containing fluid. There was a small necrotic skin area at one point. When the mass began to exude fluid, the patient was immediately operated on. The skull opening was approximately 1 cm. in diameter, and through this protruded a knuckle of bluish glistening membrane having the general appearance of a thrombosed hemorrhoid. The structure was aspirated and found to contain old blood. It was opened and examined; the inner surface had a mucosa-like pattern with numerous small villiform structures which appeared similar to the lining of the intestine. It was not removed, but a biopsy microscopic report described an area surrounded by many small thin-walled vessels reminiscent of developing choroid plexus.

Ventriculograms made five days postoperatively showed markedly dilated cerebral ventricles. No air was seen in the aqueduct or the fourth ventricle. The possibility of a mass in the posterior portion of the third ventricle was considered.

The posterior fossa and the posterior third ventricle were not explored in this patient. Choroidectomies and ventriculomastoidostomies for the hydrocephalus were unsuccessful. The child developed progressive hydrocephalus and eventually died.

In retrospect, it is possible that Case 2 and Case 3 had hemangiomatous tumors within cranial vault; this possibility was not considered at the time. We have not seen anywhere in the literature any reference to such an occurrence. Case 2 developed a progressively enlarging head without actual increase in the size of the ventricle,

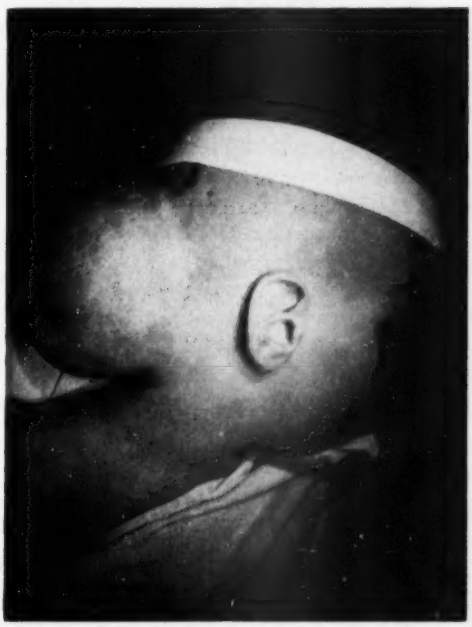

Fig. 3.—Case of cranium bifidum with an exceedingly large lesion.

and Case 3 developed a true hydrocephalus, possibly due to an expanding mass in or behind the third ventricle. Certainly a very unusual type of cyst was encountered at the first operation, but because of lack of information in the literature as to its probable significance, the cue was not followed up. The purpose of this paper is to point out the fact that at least some of these cases had best be explored intracranially at the site of the lesion or in immediate vicinity. It should also be noted that an enlarging head in association with cranium bifidum does not necessarily mean hydrocephalus.

These comments are not to be interpreted as an invitation to pessimism in the surgical treatment in cranium bifidum. Many cases treated by us have had the most favorable outcome, even in exceedingly large lesions, as shown in Figure 3.

SUMMARY

A case is presented with progressive enlargement of the head consequent to cranium bifidum which proved to have a hemangioma underlying the cranial defect rather than hydrocephalus. A search was made of the cases handled in this clinic, and two other babies were discovered whose findings were strongly suggestive of the possibility of such a lesion. Both of these children had a progressively enlarging head circumference. The inference is drawn that in certain cases intracranial exploration may reveal benign tumors associated with cranium bifidum which either are responsible for the progressive enlargement of the heads themselves or else have secondarily blocked the cerebrospinal fluid system and are responsible for hydrocephalus.

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ELECTROCARDIOGRAPHIC CHANGES DURING REPLACEMENT TRANSFUSION

Special Reference to the Effects of Serum Electrolyte Disturbances

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TWO RECENT reports * have documented electrocardiographic evidence of hypocalcemia during replacement transfusion of newborn infants with hemolytic disease of the newborn. These changes occur with normal or supernormal concentrations of total serum calcium † and are due to a low serum concentration of ionized calcium induced by the infusion of citrate contained in the donor blood.[4] We have recently encountered marked hyperpotassemia in recipient infants, resulting from exchange transfusion with donor blood which had been stored for more than 10 days.[5] It is the purpose of the present report (*a*) to present certain abnormalities of cardiac rhythm hitherto undescribed in association with replacement transfusion and (*b*) to describe and discuss the electrocardiographic manifestations of hypocalcemia and of simultaneous hypocalcemia and hyperpotassemia encountered during the procedure.

MATERIALS AND METHODS [5]

Ten newborn infants with hemolytic disease of the newborn were treated by the usual technique of replacement transfusion of citrated Rh-negative whole blood through a polyethylene catheter inserted into the umbilical vein. They ranged in weight from 1,190 to 4,250 gm., with an average weight of 3,090 gm., and in age from 2 to 36 hours, with an average age of 15 hours.

Electrocardiograms were made on each infant. Three standard limb leads and three augmented unipolar limb leads were recorded in each case immediately before and after the transfusion. Lead II was recorded during the last 5 cc. of each withdrawal and each injection of blood. All electrocardiograms were made on an Edin electronic direct-writing cardiograph. The Q-T interval and the cycle length were measured in the shortest and longest cycles in each of six limb leads in the control tracings and in each strip of Lead II obtained during the procedure. The average of the 12 measurements in the control tracings was taken for computation of the Q-T interval corrected for heart rate ($Q\text{-}T_c$ interval) according to the modified formula of Bazett.[6]

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* References 1 and 2.

† References 1-3.

Similarly, the Q-T_e interval was calculated from measurements of the Q-T interval and cycle length in the shortest and longest cycles in each strip of Lead II obtained during the transfusion. Measurements of the other components of the electrical cycle were made in the usual manner. Amplitude of the various waves was measured in millimeters and time intervals in seconds.

With two exceptions, approximately 500 cc. of blood was exchanged in each case, usually by alternate withdrawal and replacement of 20 cc. aliquots. One infant (M., Case 3) weighing 1,190 gm. was treated by replacement transfusion of 250 cc. of blood. Technical difficulties in another case (Ki.) caused the interruption of serial electrocardiograms after 100 cc. of blood had been exchanged. The procedure required from 72 to 159 minutes for completion, with an average duration of 101 minutes.

Samples of blood were obtained from the umbilical vein of all but one of the infants, just before periodic intravenous injections of 0.1 gm. calcium gluconate given as 1 cc. of 10% or 10 cc. of 1% solution. This was usually done near the end of each 100 cc. of blood exchange. A sample of plasma was obtained from each bottle of donor blood. The concentrations of sodium and potassium in the serum or plasma of these specimens were measured in a Perkin-Elmer flame photometer, with lithium as an internal standard.

RESULTS

Heart Rate.—The heart rate before, during, and after replacement transfusion are summarized in Table 1. Comparison of control electrocardiograms before and after the procedure reveals no consistent change in the rate. Heart rate was 3 to 21 beats per minute faster following the procedure in five cases, 3 to 34 beats per minute slower in the remaining six. The over-all change in heart rate between the two control tracings was less than 15 per minute in seven cases.

TABLE 1.—*Maximum, Minimum, and Average Heart Rates Encountered Before, During, and After Replacement Transfusion of Ten Newborn Infants with Hemolytic Disease of the Newborn*

	Control	1*	2	3	4	5	Control
Maximum	176	216	212	168	201	201	173
Minimum	105	102	94	82	105	56	89
Average	134	148	141	141	142	146	128

* Numerical headings indicate the corresponding one-fifth of the exchange transfusion (usually about 100 cc.).

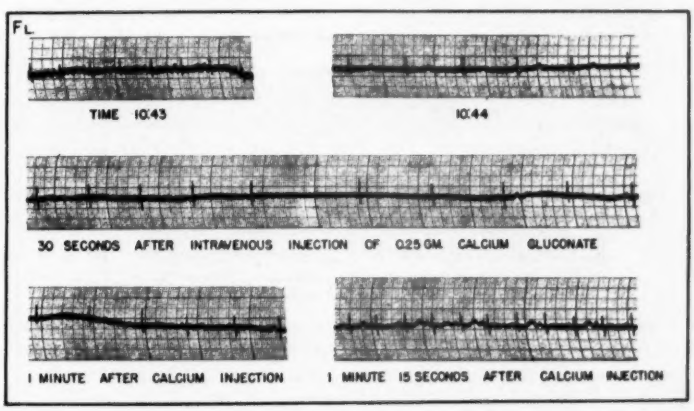
Although the heart rate of certain patients tended to increase during the injection of blood and to decrease during its withdrawal, these changes were neither consistent nor significant and were not related to the speed of injection. The fastest heart rate encountered was 216 and the slowest 56 beats per minute. The average rate on all control tracings was 131.

In general, heart rate was not influenced by a low concentration of serum ionized calcium manifested by muscle tremor or by prolongation of the R-ST segment and Q-T_e interval; nor was it affected by hyperpotassemia as determined chemically. However, the following case with these electrocardiographic changes as well as increasing hyperpotassemia experienced sudden sinus bradycardia. The intravenous injection of 0.25 gm. calcium gluconate slowed the rate further and resulted in a period of asystole for 2.04 seconds (Fig. 1).

CASE 1 (Fl.).—Birth weight 2,400 gm. The control electrocardiogram prior to exchange transfusion showed a heart rate of 104. The R-ST segment was markedly prolonged and the Q-T_e interval was 0.506. Serum sodium at this time was 147 mEq. per liter, serum potassium, 4.03 mEq.

The donor blood used in the replacement transfusion of this case was subsequently found to contain 18.24 mEq. of potassium per liter of plasma. During the first 400 cc. of the exchange, the electrocardiogram did not change significantly. Serum sodium remained stable at about 145 mEq. per liter, and serum potassium rose gradually to 6.92 mEq. (Table 2).

During the fifth 100 cc. exchange, sinus bradycardia (rate, 56) appeared suddenly without relation to the administration of calcium. At this time the P-R interval had shortened from 0.12 to 0.13 to 0.08 seconds. The P wave and T wave became lower, but the contour of the QRS complex remained unchanged. The R-ST segment and Q-T interval remained prolonged. The intravenous injection of 0.25 gm. calcium gluconate caused further slowing of the heart rate. Thirty seconds later a period of asystole of 2.04 seconds' duration occurred. Twenty seconds after this event the heart rate began to increase gradually, reaching earlier levels (105 to 110) one minute after calcium administration. Meanwhile the P-R interval had lengthened to its initial value of 0.12 to 0.13 seconds. In addition, the T wave, which had become isoelectric after the administration of calcium, regained its former contour. Serum sodium measured 146 mEq. per liter, potassium, 8.10 mEq. During the fifth 100 cc. exchange the T wave doubled its amplitude, the only electrocardiographic change suggesting hyperpotassemia seen during the procedure.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30 SECONDS AFTER INTRAVENOUS INJECTION OF 0.25 GM. CALCIUM GLUCONATE
1 MINUTE AFTER CALCIUM INJECTION
1 MINUTE 15 SECONDS AFTER CALCIUM INJECTION

Fig.1 (Case 1).—Sinus bradycardia occurring during the fifth 100 cc. exchange during replacement transfusion.

TABLE 2.—*Serum Potassium Levels During Replacement Transfusion*[*]

Case	Control	1st 100 Cc.	2d 100 Cc.	3d 100 Cc.	4th 100 Cc.	5th 100 Cc.	Donor
Fi	4.63	4.96	5.28	4.88	....	5.40	8.0
Kl	6.02	6.00	....	....	....	....	12.9
M.†	8.16	....	9.12	8.64	9.16	....	18.6
Fl	4.08	5.76	....	6.48	6.92	8.00	16.16
B	4.78	5.52	6.48	6.92	7.84	8.10	18.24
N	4.60	4.43	4.40	4.56	4.56	....	7.20
S	4.87	....	5.04	....	4.64	....	5.50
T	5.04	4.98	4.71	4.88	....	4.26	5.80
Kr	3.92	4.49	4.00	3.88	3.88	3.80	12.28

[*] Values for serum potassium given as milliequivalents per liter.
† Results for Case M. tabulated by 50 cc. rather than 100 cc. fractions of the replacement transfusion.

Heart rate from the post-transfusion control electrocardiogram was 91. The tracing was similar in all other respects to the earlier control tracing.

Repeated small intravenous injections of calcium gluconate during the replacement transfusions did not consistently slow the heart rate. Calcium administration was followed by slowing of the rate in 22 instances and by an increased rate in 8, with no change in two instances.

Rhythm.—Two patients in the present series exhibited cardiac arrhythmias hitherto undescribed in association with replacement transfusion.

CASE 2 (Fi.).—The control electrocardiogram before replacement transfusion showed a heart rate of 145 and QT_c interval of 0.400. At this time the serum sodium was 142 mEq. per liter and the potassium, 4.63 mEq. During the first 300 cc. of the exchange the electrocardiogram did not change significantly.

Parasystoles and 2:1 auriculoventricular (A-V) block occurred irregularly during the fourth and fifth 100 cc. of the exchange (Fig. 2). The arrhythmias were transitory, and they occurred without relation to calcium administration or the concentration of serum ionized calcium insofar as it is reflected by the duration of the R-ST segment or $Q\text{-}T_c$ interval. The concentration of serum potassium did not change significantly during the entire period.

The control electrocardiogram after completion of the procedure was similar to the first control tracing.

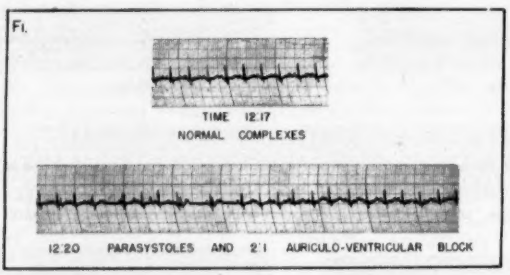

Fig. 2 (Case 2).—Transitory parasystoles and 2:1 auriculoventricular block occurring in the fifth 100 cc. exchange during replacement transfusion.

CASE 3 (M.).—Premature birth; weight 1,190 gm. Replacement transfusion was undertaken at age 24 hours. Two hundred fifty cubic centimeters of blood was used, which was subsequently found to contain 18.6 mEq. potassium per liter of plasma.

The control electrocardiogram revealed the absence of the usual neonatal right axis shift. The heart rate was 120. The R-ST segment was markedly prolonged, and the $Q\text{-}T_c$ interval was 0.556. The concentration of serum electrolytes in blood drawn before transfusion was determined later. This showed a serum sodium of 146 mEq. per liter and potassium, 8.16 mEq. Total serum calcium was 6.0 mg. per 100 cc. (3.0 mEq. per liter).

During the first 50 cc. exchange there was little change in the heart rate. The R-ST segment and Q-T interval lengthened slightly. Neither the $Q\text{-}T_c$ nor the P-R intervals could be accurately measured inasmuch as the end of the T was overlapped by the succeeding P wave. Late in this period the P and T waves were almost completely superimposed, particularly in tracings made during the injection of blood.

Early in the second 50 cc. exchange the above changes advanced until the P wave was indistinguishable from the preceding T wave. Midway in this period transient muscle tremor was first noted simultaneously with an increase in amplitude of the "T-P" wave from 1.8 to 3.3 mm. This was followed within 10 seconds by the sudden onset of 2:1 A-V block with an auricular rate of 132 and a ventricular rate of 66 beats per minute. Muscle tremor disappeared 10 seconds after the onset of 2:1 A-V block. The exchange transfusion was temporarily interrupted because of the arrhythmias, but A-V block continued unchanged for about four minutes. The intravenous injection of 0.1 gm. calcium gluconate restored sinus rhythm immediately. The R-ST segment appeared relatively shorter. The heart rate was 90, and the P-R interval, 0.10 seconds. Transient multifocal nodal beats then occurred with corresponding variation in

the P wave, P-R interval, and QRS complex. The heart rate slowed to 79. During the succeeding five minutes 0.4 gm. calcium gluconate was injected intravenously in intermittent doses of 0.1 to 0.2 gm. Sinus rhythm was restored two minutes after interruption of 2:1 block. The rate was 132, the P-R interval, 0.10 seconds, the QRS time, 0.05 seconds, and the T wave was almost isoelectric. The replacement transfusion was then resumed, and the T wave gradually gained in amplitude to 1.0 mm. Calcium administration had slightly shortened the R-ST segment, permitting separation of the T and P waves. The Q-T_c interval was 0.472. Figure 3 illustrates the electrocardiographic changes described. Subsequent measurement of the serum electrolytes

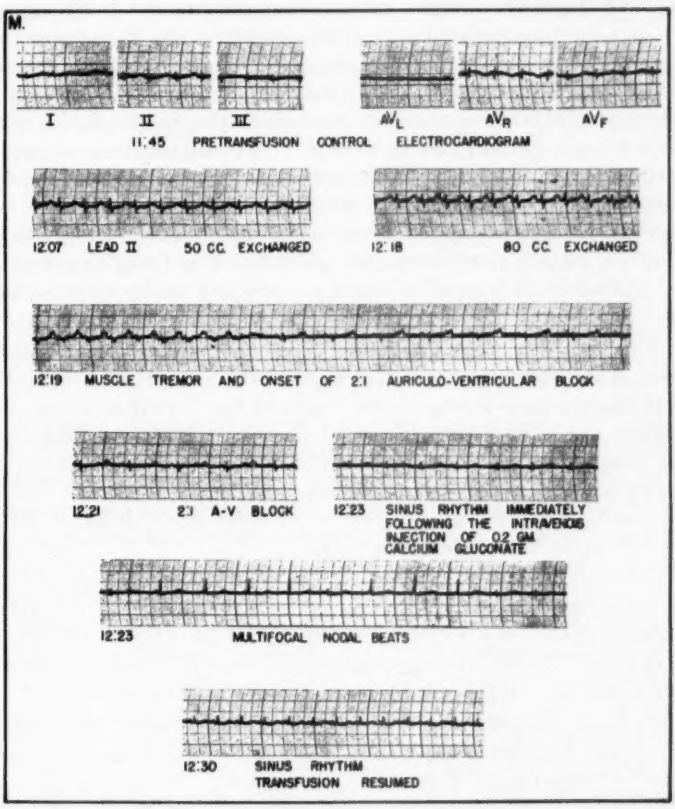

Fig. 3 (Case 3).—Electrocardiographic changes during replacement transfusion for hemolytic disease of the newborn.

in blood obtained just before the onset of 2:1 block revealed a potassium concentration of 9.12 mEq. per liter and a total calcium of 6.4 mg. per 100 cc. (3.2 mEq. per liter).

The electrocardiogram remained essentially unchanged during the remainder of the replacement transfusion. During the third 50 cc. of the exchange, serum potassium was 8.64 mEq. per liter, and total calcium, 13.6 mg. per 100 cc. (6.8 mEq. per liter). Serum potassium rose to 9.16 mEq. per liter during the fourth 50 cc. exchange, and the total calcium was 11.6 mg. per 100 cc. (5.8 mEq. per liter).

The electrocardiogram after the procedure showed a heart rate of 122 and a Q-T_c interval of 0.476, with a somewhat shorter R-ST segment than in the pretransfusion control tracing.

The patient died within 24 hours of the replacement transfusion. Postmortem examination revealed the findings of prematurity and of severe hemolytic disease of the newborn, including kernicterus. The heart was not abnormal in structure. Histological examination‡ showed slight vacuolization of muscle fibers and mild interstitial edema. These changes are nonspecific and are encountered in the hearts of most infants dying early in the neonatal period.

The P Wave, P-R Interval, and QRS Complex.—Abnormalities of these determinants were not encountered except in association with the wandering pacemaker in Case 3 (above).

The R-ST Segment.—Unmistakable prolongation of the R-ST segment was observed at some time during the procedure in every case except one (Ki). To the extent that it may reflect a low concentration of serum ionized calcium, prolongation of the R-ST segment was an earlier and more consistent finding than electrocardiographic evidence of muscle tremor indicating heightened neuromuscular irritability. Pronounced lengthening of the R-ST segment occurred without evidence of muscle tremor in some cases. Clinical tetany did not occur in the present series, even with lengthening of the R-ST segment to the point of 2:1 heart block (Case 3). In general, the duration of the R-ST segment is reflected in the magnitude of the Q-T_c interval (below), since the contour and duration of the QRS complex and T wave are unaltered. There was no significant elevation or depression of the R-ST segment, even with pronounced hyperpotassemia.

The T Wave.—The contour and duration of the T wave did not change significantly despite the wide electrolyte fluctuations. Two patients with induced hyperpotassemia showed some increase in the height of the T wave as serum potassium concentration rose. The T wave of Case 3, however, declined in amplitude despite sustained hyperpotassemia. In our patients the intravenous injection of small doses of calcium gluconate usually caused transient lowering of the T wave. The T wave was consistently taller during the injection of blood than during its withdrawal, regardless of serum electrolyte concentrations.

The Q-T_c Interval.—Initial control tracings exhibited a maximum Q-T_c interval of 0.556, a minimum of 0.404, with an average of 0.445. The Q-T_c interval on tracings made after completion of the procedure varied from 0.395 to 0.514, with an average of 0.439. During exchange transfusion, the Q-T_c interval varied greatly between a minimum of 0.344 and a maximum of 0.564. The average Q-T_c interval was slightly longer during the injection of blood than during its withdrawal.

The repeated injection of small doses of calcium during replacement transfusion consistently shortened the Q-T_c interval (average, 6.6%) by transient but significant shortening of the R-ST segment. We were unable to relate the amount of shortening to the dose of calcium administered, to the initial length of the R-ST segment, or to serum levels of sodium or potassium. The responses were brief and usually disappeared within two or three minutes or when the transfusion was resumed.

Electrolytes.—The concentration of serum sodium remained within normal limits or was slightly elevated before, during, and after replacement transfusion in the six cases in which it was measured. Values ranged from 144 to 153 mEq. per liter, with an over-all average of 148 mEq.

Table 2 summarizes the concentration of serum potassium before, during, and after replacement transfusion in nine cases, and also indicates the concentration of

‡ Sections examined by Dr. Charles L. Yuile, Department of Pathology.

this ion in the plasma of the donor blood. Hyperpotassemia was induced in two cases (Fl. and B.) by replacement transfusion with donor blood containing more than 16 mEq. potassium per liter of plasma. The serum potassium of a third infant (M., Case 3, above) was 8.16 mEq. per liter before transfusion. The baby was premature and received donor blood containing 18.6 mEq. potassium per liter of plasma. The serum potassium concentration rose to 9.16 mEq. per liter during the fourth 50 cc. of the exchange, the highest concentration of serum potassium encountered in a recipient infant. One patient (Kr.) maintained a stable normal serum potassium level despite replacement transfusion with donor blood containing 12.28 mEq. potassium per liter of plasma.

Total serum calcium was measured in three cases. Patient Fi. showed a rise from 7.6 to 10.0 mg. per 100 cc. (3.8 to 5.0 mEq. per liter) during the exchange transfusion. Patient Ki. had a concentration of 10.0 mg. per 100 cc. (5.0 mEq. per liter) at the conclusion of the procedure. Patient M. (Case 3, above) had an initial total serum calcium of 6.0 mg. per 100 cc. (3.0 mEq. per liter), which later rose to 11.6 mg. (5.8 mEq.). Before transfusion this patient had a prolonged R-ST segment and Q-T_c interval (0.556), which remained abnormally long throughout the procedure despite the injection of large doses of calcium gluconate. No relation was observed between the length of either the R-ST segment or the Q-T_c interval and the concentration of total serum calcium during or following replacement transfusion.

COMMENT

The content and concentration of intracellular electrolytes and their electrochemical relation to extracellular electrolytes across the myocardial cell membrane are probably of first importance in producing the electrocardiographic changes characteristic of various electrolyte disturbances. The nature of changes occurring at the myocardial cell membrane is unknown. The rapid changes of several electrolytes during replacement transfusion of patients in the present series undoubtedly complicate these effects.

Lengthening of the R-ST segment with consequent prolongation of the Q-T interval has been repeatedly observed with low concentrations of total serum calcium.§ Yu [7] found a significant correlation between the concentration of total serum calcium and the duration of the R-ST segment and Q-T_c interval in a series of patients with disturbances of calcium metabolism. It has been suggested that these changes parallel the serum concentration of calcium ion rather than total calcium.‖ McLean and Hastings [12] have shown that calcium ion concentration in serum is usually related to total serum calcium and protein concentration. However, with the introduction of citrate, calcium is bound and hence no longer contributes calcium ions. During replacement transfusion, infusion of large amounts of citrate will reduce the concentration of ionized calcium, although total serum calcium concentration may remain unchanged. This explains our finding and that of others ¶ that electrocardiographic changes may suggest alterations in the concentration of serum ionized calcium without relation to total serum calcium in these exceptional circumstances. The intravenous injection of calcium ions (as calcium gluconate) reversed

§ References 7-11.

‖ References 1, 2, and 4.

¶ References 1, 2, and 4.

the electrocardiographic changes immediately, though transiently. Until comparative measurements of calcium ion concentration are made, the reliability of the electrocardiogram as a measure of ionized calcium will be speculative. Muscle tremor as an indication of low serum ionized calcium # was usually noted in active irritable infants or doing the rapid injection of blood and was not uniformly associated with prolongation of the R-ST segment and Q-T interval. Tetany was not encountered even with pronounced electrocardiographic changes.

The two cases which developed hyperpotassemia showed some increase in the amplitude of the T wave, although its contour and duration did not change. The case of sustained hyperpotassemia, however, showed a decrease in the height of the T wave during the procedure. Other electrocardiographic evidence of hyperpotassemia * was not observed. "Tent-shaped" T waves, recently proposed by Levine [13] as a more subtle indication of potassium intoxication under certain circumstances, were not seen. The studies of Finch and associates [19] suggest that more consistent and characteristic T-wave alterations might have been found if precordial leads had been recorded.

Ringer's classic description of the antagonism of calcium and potassium on heart muscle [20] has recently been extended by Levine and co-workers,[13] who showed that normal serum calcium antagonizes and low serum calcium enhances electrocardiographic abnormalities associated with potassium intoxication. However, to the extent that prolongation of the R-ST segment and Q-T interval parallel low serum concentration of ionized calcium, electrocardiographic evidence of hyperpotassemia was not augmented in the present patients.

Similarly, normal serum sodium concentration has been shown to antagonize and a low sodium to enhance electrocardiographic effects of hyperpotassemia.[21] Normal serum sodium in the present cases may account in part for the minimal electrocardiographic evidence of intoxication in our patients with induced hyperpotassemia.

The present study confirms the findings of Gustafson [2] that heart rate is not consistently affected by the exchanges of blood, that the speed of injection does not influence the incidence of electrocardiographic abnormalities, that more rapid injection causes more muscular activity and irritability occasionally associated with sinus tachycardia, and that the electrocardiogram following replacement transfusion does not differ, in general, from the pretreatment control tracing.

SUMMARY AND CONCLUSIONS

Studies of the electrocardiogram with reference to serum electrolyte changes are reported in 10 newborn infants during replacement transfusion for hemolytic disease of the newborn.

1. Heart rate was labile and showed little predictable change. Intravenous calcium gluconate did not consistently slow the rate. Pronounced sinus bradycardia with shortening of the P-R interval occurred in one case and could not be clearly related to the coincident hypocalcemia and hyperpotassemia.

2. One case exhibited transient parasystoles and partial auriculoventricular block without relation to changes in serum electrolytes.

References 1 and 2.

* References 13-18.

3. Prolongation of the R-ST segment and Q-T_c interval suggesting deficiency of ionized calcium induced by infusion of citrate occurred in all but one of the cases. Muscle tremor was inconstant, and tetany was not observed. The level of total serum calcium was measured in three cases and did not parallel the electrocardiographic changes. One patient with pretransfusion hypocalcemia showed progressive lengthening of the R-ST segment and Q-T interval until 2:1 auriculoventricular block occurred. This was dramatically relieved by the injection of calcium gluconate.

4. The T wave was consistently taller and the Q-T_c interval longer during the injection of blood than during its withdrawal.

5. Hyperpotassemia was induced by replacement transfusion in two cases and was present in a third before transfusion. Hypocalcemia coexisted in each case. Increased amplitude of the T wave was the only electrocardiographic characteristic noted in the two cases of induced hyperpotassemia. Serum sodium was normal or slightly increased in all cases.

6. The occurrence of electrocardiographic changes in association with serum electrolyte disturbances emphasizes, first, the need for periodic injections of calcium gluconate during the procedure to minimize the hazard of hypocalcemia, and, second, the importance of using fresh donor blood in order to avoid hyperpotassemia.

7. Further studies are needed to define the nature, cause, and treatment of the cardiac arrhythmias encountered during replacement transfusion and to evaluate the cardiac and metabolic effects of associated electrolyte disturbances. Until the incidence and significance of these changes is more clearly defined, it is recommended that a direct-writing electrocardiograph be connected to the patient during replacement transfusion so that immediate records can be obtained either at specified intervals or as indicated.

Dr. A. B. McCoord performed the electrolyte analyses, and Mrs. J. N. Gooding prepared the manuscript. The Pediatric Resident Staff and the late Dr. S. W. Clausen also helped with the study.

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Case Reports

PIEBALDNESS, OF FAMILIAL WHITE SKIN SPOTTING (PARTIAL ALBINISM)

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AND
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OMAHA

PIEBALDNESS, or familial white skin spotting, is a congenital defect of skin pigmentation which is of rare occurrence, inherited as a dominant characteristic. It is characterized by a defect in skin pigment which may involve the central portion of the brow, including a small portion of the scalp, with a resulting white forelock, areas on the anterior surface of chest, abdomen, and extremities, but with no involvement of the remainder of the face or back. The skin defects remain throughout life and are constant. The brow defect is usually triangular or diamond-shaped, and the eyebrows may be involved with white hairs. The depigmented areas of the extremities are usually bilateral, although not symmetrical, and may show much variety in extent and shape with clearly demarcated skin lines. The extremities and trunk may show small islands of normal pigmented skin within the depigmented area, varying in size from a few millimeters to several centimeters. The feet, ankles, hands, and wrists seem to be less involved. There are no mental or other physical defects.

The trait is usually due to a dominant gene with complete penetrance, therefore, once it is lost in an offspring, it does not reappear. It is not to be confused with albinismus universalis, which is a melanin defect not only of skin but also of choroid and hair, often associated with mental deficiency; this is due to a hereditary recessive factor. Nystagmus and photophobia, when present are due to the absence of protective pigment in the choroid. The lack of pigment in either piebaldism or total albinism is thought to be due to a failure to form brown or black melanin pigment from tyrosine. In the complete albino, this lack of pigment is believed to be due to a hereditary absence of the enzyme tyrosinase, which acts as a catalyst in a series of reactions transforming tyrosin to melanin. In piebaldism, only the pigmented skin contains tyrosinase. Here the anomaly is one of distribution of pigment.

There are 23 families reported in the literature; this report (the 24th) consists of a Negro mother and her three children. We suspect that partial albinism is much more common than the literature indicates. The mother included in the present description showed considerable surprise over our interest in the white spots. She had been to many doctors, she stated, and had visisted numerous clinics at various times for general medical care, but no one had ever asked her about her own skin defect or that of her offspring. Indeed, records of various hospitals where Mrs. G. or any of her children had been admitted as patients fail to even mention the skin anomaly which first strikes the examiner's eye.

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Dennis G. (Fig. 1), a 4-month-old Negro boy, entered Children's Memorial Hospital on Aug. 6, 1953, with the chief complaint of vomiting and diarrhea of four days' duration. Two days prior to admission, the mother stated that she was unable to get any formula or liquid to stay down, and stools averaged 12 to 15 per day and were yellow-green and foul-smelling.

Past history disclosed that the child was born normally, had developed normally, and had had no past illnesses.

Physical examination revealed a well-developed infant, apparently of stated age, showing a moderate degree of dehydration and a temperature of 101 F. The anterior fontenel was slightly depressed, and there was moderate diminution of skin turgor. The remainder of the physical examination was within normal limits except for the skin. The infant has a striking appearance, with the central area of the forehead showing a diamond-shaped area of completely depigmented skin measuring 5 cm. by 3.25 cm. extending to 1 cm. behind the hair line, the hair in this area being white. The medial part of both eyebrows showed completely white hairs.

Figure 1

The chest and abdomen revealed large depigmented areas of skin extending in a wedge-shaped pattern; inside this large island of depigmented skin there was one round small area of normal pigmented skin measuring 1 cm. by 1¼ cm. Both upper arms on the medial surface showed large irregular-shaped depigmented areas. The right leg showed a white encircling area beginning at the knee and extending to the lower midleg, with two small normally pigmented areas measuring 0.5 cm. by 0.5 cm. The left leg revealed the same general distribution, with small islands of pigmented tissue; however, the depigmented surface also extended upward to the medial aspect of the upper thigh, ending in a point. There were no depigmented areas on the back, ankles, feet, hands, or wrists.

The mother stated that the white skin areas had been present since birth and had shown no change. She stated that her two older children had similar skin defects.

The oldest child, Walter G. (Fig. 2), age 7 years, weight 63¾ lb. (28.7 kg.), height 51 in. (129.5 cm.). Physical examination was within normal limits except for the skin. The forehead had a central depigmented area, wedge-shaped, and involving 1.5 cm. of the scalp, with a white forelock. The medial part of both eyebrows showed completely white hairs. The abdomen and

thorax were involved with a large irregularly shaped depigmented area extending from the nipple line to 4 cm. below the umbilicus. In this area were a total of 37 small normal appearing islands of pigmented skin varying in size from a few millimeters to 2 cm. by 2 cm. Both upper arms and elbows had depigmented areas of irregular shape on the medial surface. Both thighs on the medial surfaces showed irregular areas of depigmented skin, the right thigh area having numerous small islands of pigmented skin.

Robin G., age 2½ years (Fig. 2), weight 36½ lb. (16.5 kg.), height 37 in. (94 cm.). The physical examination was within normal limits except for the skin. The forehead showed a central depigmented area 3 cm. by 1.5 cm., diamond-shaped, and involving 1 cm. of the scalp, with a resulting white forelock. The medial part of both eyebrows showed completely white hairs. The right arm had a spiral depigmented area extending from the elbow to the mid-anterior surface of the forearm. The left arm had a similar spiral depigmented area but also had two small round islands of pigmented skin. The upper right lower leg had an encircling

Figure 2

band of depigmented skin with numerous pigmented islands. The left leg was similarly involved, but the area was wider and extended for several centimeters along the knee. The abdomen and chest were not involved in this child. The back, ankles, feet, wrists, and hands were also not involved.

Mother, Mrs. G. (Fig. 1), aged 25 years. Physical examination was within normal limits except for the defects of the skin. The forehead showed a central depigmented area, wedge-shaped, 7 cm. by 7 cm., involving 1 cm. of the scalp, with a white forelock. The medial part of the eyebrows contained white hairs. There was an area of depigmentation about the size of a quarter under the chin. The abdomen and chest showed large areas of depigmented skin, with numerous small round islands of normal pigmented skin. The arms had encircling bands involving the hind and upper part of the lower legs, which were similar in appearance to Robin's.

Past history revealed that Mrs. G. had a miscarriage in 1947, at approximately six months' gestation, a baby girl which lived only a few hours. The mother (unfortunately for this report) does not know whether there were any skin defects on this fetus, and the hospital chart contains no description of the skin, nor is there a record of Mrs. G.'s peculiar skin anomaly. Mr. G.

was in good health and has no skin defects or abnormal pigmentation. As far as Mrs. G. knew, she was the only one in her family to have any skin defects; her parents and grandparents were normal. Mrs. G. had two brothers and five sisters, all of whom had children. These children were all normal, except for one sister, who had a 14-year-old boy with a small white spot on the side of the neck, which was present at birth; he had no other skin defects and no white forelock.

SUMMARY

A family of piebalds is reported, showing the hereditary factor operating in a mother and her three children. This family presents a striking appearance, in which the forelock and characteristic pattern of depigmented skin are evident.

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CHRONIC PULMONARY DISEASE DUE TO NOCARDIA

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WE ARE reporting the following case of pulmonary nocardiosis with multiple metastatic abscesses because it presented a difficult problem in diagnosis and because it had an unusual origin in severe disease of the lung in a child.

REPORT OF CASE

Clinical Aspects.—A boy, 15 months old, was admitted to a hospital in Indiana on Dec. 6, 1952, because of a respiratory infection of about 10 days' duration. At the onset, the patient had contracted what was thought to be a head cold, although he previously had manifested a productive cough. There was a moderate elevation of temperature accompanied by cough and wheezy respiration, pallor, listlessness, and loss of strength. A mild blueness developed around the lips and eyes. Vomiting had been periodic, and the cough was much worse at night. The feeding habits of this child had always represented a problem. He had been in a hospital because of feeding difficulties and diarrhea from the age of 3 to 6 months. He had been better, except for his respiratory infection and cough, during the six weeks prior to his admission at the age of 15 months. A skin rash, which developed while the infant had been previously hospitalized, was thought to be atopic eczema.

During the fall of 1952, he had suffered from convulsions and high fever and had been in the hospital for nine days.

A sister, 2 months old, seemed to be normal.

Examination disclosed moderate infection of the upper part of the respiratory tract, with diffuse wheezing throughout the entire thorax but no respiratory distress. A roentgenogram of the thorax disclosed extensive bilateral pneumonia. Another roentgenogram, made five days later, showed no essential change. Results of urinalysis were negative. The value for hemoglobin was 13.5 gm. per 100 cc. of blood, erythrocytes numbered 4,540,000 per cubic millimeter and leucocytes 15,800, with 91% polymorphonuclear cells and 9% small lymphocytes. The coagulation time was 3½ minutes. Two days later, the count was almost identical, except for a decrease in polymorphonuclear cells to 84%. Four days later, the leucocyte count had dropped to 6,200 per cubic millimeter of blood, with 92% polymorphonuclear cells. Culture of swabbings from the throat produced Gram-positive cocci in pairs. Results of sensitivity tests on these organisms showed resistance to chlortetracycline (Aureomycin), oxytetracycline (Terramycin), and chloramphenicol, with slight sensitivity to penicillin, streptomycin, and bacitracin. The organisms were thought to be a viridans Streptococcus. Culture of material obtained at coughing did not yield Hemophilus pertussis. At the time of admission, the child's temperature was 103.2 F., but on the next day it decreased to normal and remained so.

Recurrent cyanosis was most marked around the lips. At times, respirations became grunting and rather difficult. One teaspoonful (4 to 5 ml.) of a suspension of oxytetracycline was administered orally every four hours, and a hypoallergenic formula (Nutramigen) was employed. The patient was dismissed on Dec. 11, 1952.

From the Section of Bacteriology (Dr. Weed) and the Section of Pediatrics (Dr. Keith), Mayo Clinic.

This patient was readmitted on Dec. 25, when, after a period of four days of well-being, fever and difficulty in respiration developed. The cough became intensified, and there were râles in both lungs, with consolidation, especially on the left side. There was little cyanosis. Reaction of a histoplasmin test was negative, and examination of the esophagus with opaque medium (iodized oil U. S. P. [Lipiodol]) showed no evidence of a fistula. The child's weight at the second admission was 19 lb. 4 oz. (8,730 gm.).

A roentgenogram of the thorax showed no essential change from the previously described extensive bilateral pneumonitis. The patient's temperature on admission was 102.6 F., but this decreased to normal on the next day and remained so until Dec. 30, when it increased to 101 F. Thereafter, the temperature was normal. The urine was clear except for a few leucocytes. The value for hemoglobin was 13 gm. per 100 cc. of blood. The erythrocyte count was 4,180,000 per cubic millimeter of blood, and the leucocyte count, 18,900, with 79% polymorphonuclear cells. Four days later, the leucocyte count had decreased to 5,650. Urinalysis done later showed hematuria of Grade 1 +, but this cleared rapidly. Trypsin activity in the stool was positive in 1:10 dilution. Total fat content of the stools was 18% (10% fatty acids and 8% neutral fat). The patient was placed in an oxygen tent, and a suspension of oxytetracycline was administered orally. He seemed to improve rather rapidly. He was dismissed on Jan. 12, 1953.

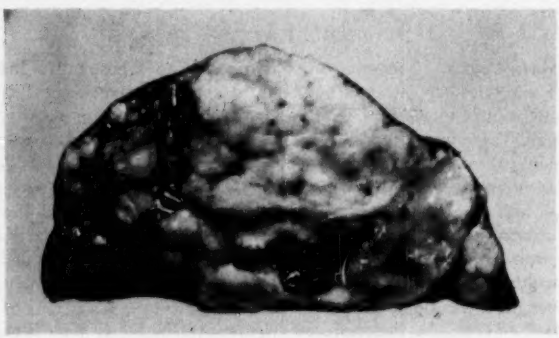

Fig. 1.—Cut surface of the lung. Note the nodules of varying size resembling masses of tumor.

The child was then admitted to a hospital in Rochester, Minn., on Jan. 14, 1953. At this time he weighed 23½ lb. (10,660 gm.) and appeared to be chronically ill. There were crepitant râles throughout the lung fields on both inspiration and expiration. The abdomen was somewhat distended, but there was no tenderness or rigidity, and no masses were found. Results of a rectal examination were negative. It was felt that the child's condition at this time was consistent with a diagnosis of fibrocystic disease of the pancreas.

Urinalysis gave negative results. The value for hemoglobin was 13.6 gm. per 100 cc. of blood, erythrocytes numbered 4,420,000 per cubic millimeter and leucocytes 15,800, with 33% lymphocytes, 54% neutrophiles (segmented), and 13% band forms. Roentgenograms of the thorax showed bilateral pulmonary fibrosis. Roentgenograms referred from Indianapolis and dated Jan. 12, 1952, to Jan. 5, 1953, showed that the bilateral pulmonary fibrosis had not changed appreciably during this interval. In a roentgenogram dated Feb. 28, 1952, superimposed bronchopneumonia was evident.

Fluid from the duodenum was obtained; the pH was 7.5; bile was present. Trypsin also was present to the equivalent amount of 2 cc. of N/10 solution of potassium hydroxide. Diastase was reported as 0.7 gm. of maltose. Lipase activity was represented by the figure of 246 cc. of N/20 solution of potassium hydroxide. These findings ruled out the presence of cystic fibrosis of the pancreas.

Results of a histoplasmin test and a coccidioidin test were negative on Jan. 19. A Mantoux test gave negative results. On Jan. 21, the stool contained 80.7% total fat. Results of blood culture were negative.

Bronchoscopic examination was considered, but before this was done the child's temperature increased from a relatively low level of less than 100 to 103 F. The respirations were 60 per minute. Crepitant rales were heard throughout both lungs, and cyanosis developed when the child cried. At this time, a roentgenogram of the lungs showed a diffuse, patchy pneumonitis in addition to the previous fibrosis. The child was treated with penethamate hydriodide

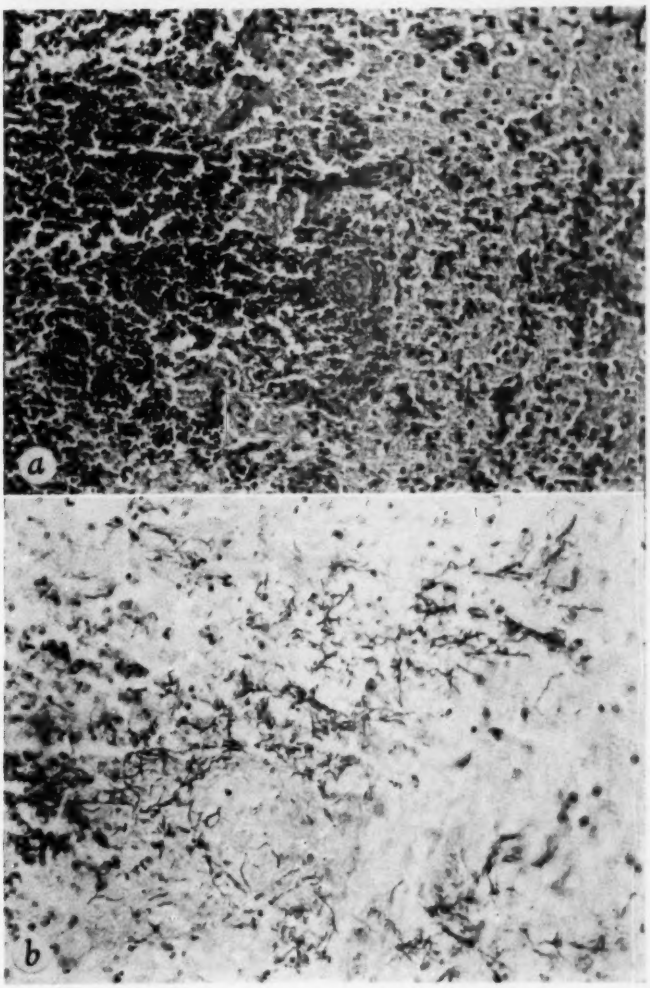

Fig. 2.—(*a*) Margin of an abscess in the brain. Note that as in Figures 3*a* and 4*a* there is no evidence of beginning encapsulation (hematoxylin and eosin, × 140). (*b*) Margin of the abscess shown in Figure 2*a*, but stained with the Brown-Gram technique. Note again that the filaments are at the margin of the abscess and appear to be invading the brain substance (× 265).

(Neo-Penil), oxygen, and penicillin aerosol. The temperature remained elevated, and the child's condition became serious.

Fifteen milligrams of cortisone was administered intramuscularly daily. The liver then became enlarged and somewhat tender. The pulse rate was 192 per minute. An electrocardio-

gram showed evidence of left ventricular preponderance. A roentgenogram of the thorax showed the heart to be enlarged; it was felt that there was a possibility of early cardiac failure. Digitalis was then administered, and an electrocardiogram was repeated. This time it showed minor right ventricular preponderance. Considerable abdominal distention occurred, increasing the child's distress. The enlargement of the liver decreased during the next few

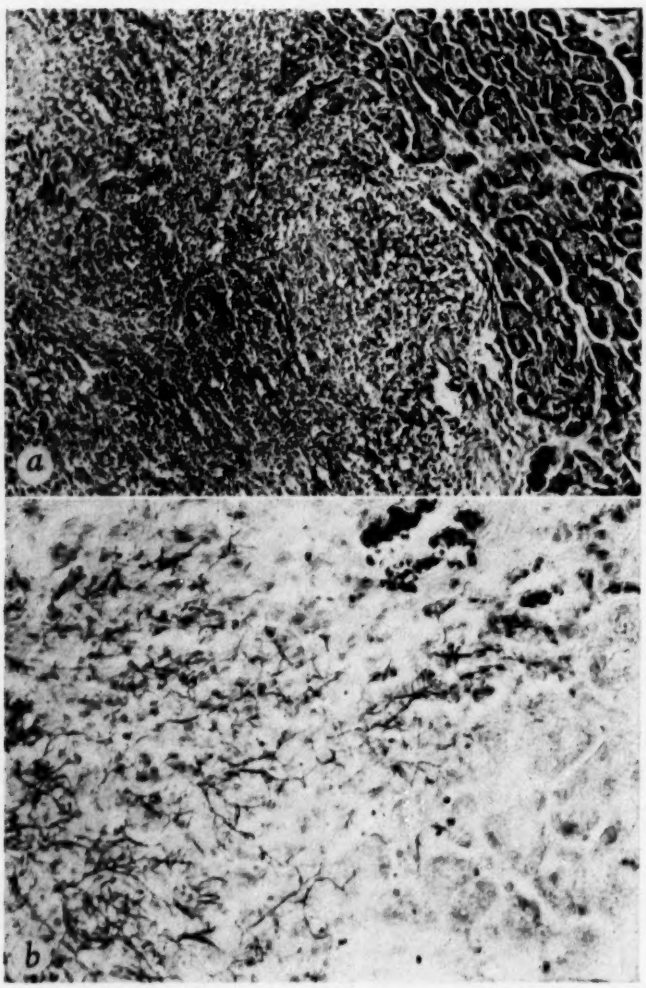

Fig. 3.—(*a*) Margin of the abscess in the pancreas (hematoxylin and eosin, × 105). Note the absence of visible filaments. (*b*) Margin of the abscess shown in Figure 3*a*, but stained by the Brown-Gram technique. Note that the filaments are at the margin of the abscess and invading the faintly stained pancreatic parenchyma and that in this area few leucocytes are present (× 310).

days. The temperature persisted at a relatively high level of between 101 and 105 F. Respiratory distress increased. Because of the effect of digitalis as demonstrated in the electrocardiogram and a decrease in the size of the liver, the use of digitalis was discontinued. The condition of the patient became critical. He died on Feb. 4, 1953.

Pathologic Aspects.—The important anatomic abnormalities were found in the lungs, brain, pancreas, and skeletal muscles.

The right and left lungs weighed 138 and 152 gm., respectively, and the parenchyma had been largely replaced by numerous ill-defined, solitary and conglomerate, firm grayish-white nodular masses a few millimeters to several centimeters in diameter. The masses projected

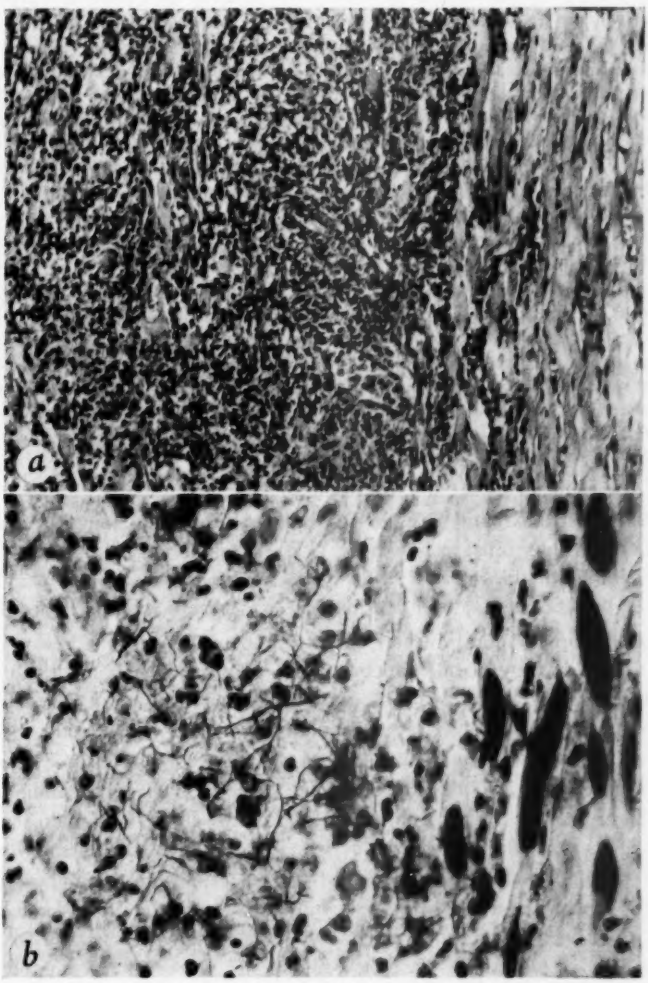

Fig. 4.—(*a*) Margin of an abscess in the intercostal muscle (hematoxylin and eosin, × 165). No filaments are visible with this stain. (*b*) Margin of the intercostal abscess shown in Figure 4*a*, but stained by the Brown-Gram technique. Note that the fine branching filaments are growing at the outer margin of the leucocytic infiltration. Very few filaments were found in the center of the abscesses. No masses of filaments (sulfur granules) like those seen in actinomycosis were found (× 550).

above the pleural and cut surfaces and grossly had the homogeneous shiny appearance suggestive of lymphosarcoma. The central portion of one of the larger masses was soft and friable and contained a coarsely granular grayish-white material resembling tumor tissue undergoing liquefactive necrosis. The similarity to tumor tissue is shown in Figure 1.

The brain was found to contain a grayish-white firm nodule 5 mm. in diameter immediately beneath the leptomeninges on the inferior surface of the left frontal lobe. Similar-appearing nodules were seen in the meninges over the temporal poles.

The tail of the pancreas contained a solitary ill-defined firm yellowish-white area 6 mm. in diameter. There was an occasional firm white nodule 1 to 2 mm. in diameter in the intercostal muscles. No recognizable gross lesions were found in the remaining organs.

The lesions in the lungs, brain (Fig. 2*a* and *b*), pancreas (Fig. 3*a* and *b*) and intercostal muscles (Fig. 4*a* and *b*) had essentially the same histopathologic features; namely, necrosis with suppuration characterized by infiltration of neutrophilic polymorphonuclear cells and macrophages. Granulation tissue was present in varying amounts, but the walling-off process was scattered and mild in degree. Multinucleated giant cells were conspicuously absent. Tubercle formation was not found. In the preparations stained with hematoxylin and eosin no organisms were found, but in similar sections stained by the Brown-Gram technique many fine-branching filaments approximately 1 μ in diameter were found (Figs. 2*b*, 3*b*, and 4*b*). Curiously, these filaments were very numerous in the walls of the abscesses near the junction of the necrotic with the normal tissue, where leucocytic infiltration was minimal. There were very few filaments in the pools of pus making up the central portions of the abscesses.

The histologic sections suggest that the filaments grew by direct extension into or between the tissue cells, produced the necrosis, and were destroyed by the infiltrating phagocytes. Sections of the lungs contained numerous filaments in the alveoli and the bronchioles, even though necrosis had not yet developed. Smears made from the exudate in the main bronchi and trachea were found to contain many filaments similar to those found in the abscesses. Culture of material taken from various parts of the lungs demonstrated Nocardia asteroides. No other organism could be demonstrated by smear, culture, or inoculation of animals.

COMMENT

This case illustrates many of the important features of pulmonary nocardiosis: (1) chronicity, with gradual progression; (2) multiple lesions; (3) failure to show resolution after antibiotic therapy; (4) correct diagnosis frequently not made by routine procedures, and (5) eventual multiple widespread metastatic abscesses.

Most of the foregoing are interrelated but are dependent on the failure to establish early the true nature of the etiologic agent. The situation is made worse when the patient is an infant or child who is not capable of complete cooperation to provide suitable specimens of sputum. Even if sputum is produced and collected in adequate amounts, routine bacteriologic examination frequently may fail to demonstrate Nocardia organisms unless the plates are held for a few days and examined specifically for the organism. Most specimens of sputum are likely to contain micrococci, streptococci, species of Hemophilus, Neisseria, and other organisms which will appear after short incubation and mislead the bacteriologist unless he knows the condition is unusual and needs special study. If sputum is not available, either because it is not being produced or because the patient cannot cooperate, the question might be raised as to whether bronchoscopy should not be done routinely for any patient who has an intrapulmonary process which does not respond to antibiotic therapy in a short time. If, by such examination, a local lesion cannot be found at biopsy or by study of aspirated secretions, it would be well to irrigate the proper bronchi with saline solution and use the return fluid for culture.

The correct diagnosis, if made early, not only gives a better chance of cure but may prevent serious complicating metastatic lesions which frequently occur in suppurative disease of the lung, regardless of the cause. Like the diagnosis of most chronic infections, the correct diagnosis of nocardiosis of the lungs depends on proper

material for study in adequate amount and thorough bateriologic examination. By the time such a condition has become chronic, it will have become evident that routine procedures are and have been inadequate. Hence, in order not to jeopardize life, drastic procedures might well be considered. If a satisfactory specimen of sputum can be obtained, extensive studies should be made to determine the proper causation, because the patient's life depends on it.

A complete description of Nocardia asteroides can be found in "Bergey's Manual of Determinative Bacteriology," but a few words about the organism are worth emphasizing. It is a filamentous organism, usually Gram-positive but sometimes Gram-negative. Frequently it is granular in its staining reaction. The filaments fragment into coccoid and bacillary forms. The organism for a long time was considered to be the "aerobic Actinomyces," in contradistinction to the "anaerobic Actinomyces" associated with lumpy jaw. Nocardia asteroides does resemble the organism of actinomycosis somewhat, morphologically, but the two are entirely different in their distribution in nature, their cultural features, the disease produced, and their response to chemotherapy.

Actinomycosis generally is best treated with penicillin, chlortetracycline, or oxytetracycline, but, since it is usually a mixed infection, some form of combined therapy may be needed. Actinomyces organisms, however, are sensitive to these agents. Nocardiosis, on the other hand, usually responds better to sulfonamide therapy. It is, therefore, natural, logical, and advantageous to use the name "nocardiosis" for the disease produced by species of Nocardia.

Some strains of Nocardia are slightly acid-fast, and the bacillary forms may be mistaken for tubercle bacilli. The strain involved in the present case was sufficiently acid-fast that a Ziehl-Neelsen stain of the material from the bronchus or trachea might have led to the erroneous diagnosis of tuberculosis. A careful observer, however, would have recognized the presence of many acid-fast coccoid forms and suspected nocardiosis. This is one of the reasons we rely on culture in preference to smears stained for acid-fast bacilli.

SUMMARY AND CONCLUSIONS

A case of pulmonary nocardiosis with metastatic abscesses is reviewed, with presentation of the clinical and necropsy findings.

The problems relating to early and accurate determination of the nature of the etiologic agent in suppurating disease of the lung are discussed. The importance of such information is emphasized.

Routine bacteriologic examination of sputum may fail to demonstrate Nocardia organisms. The reasons for this are discussed. It is therefore recommended that the condition of patients with infection of the lung who do not respond to antibiotic therapy be studied extensively to determine the nature of the etiologic agent. Such efforts may not only save a patient's life but may prevent the crippling effects of metastatic abscess which frequently occurs when such a disease becomes chronic.

Society Transactions

AMERICAN PEDIATRIC SOCIETY

Rustin McIntosh, M.D., *President*

Sixty-Fourth Annual Meeting

Buck Hill Falls, Pa., May 3, 4, and 5, 1954

(Concluded from Page 396)

Acute Disseminated Reticuloendotheliosis. Dr. Amos Christie, Dr. Randolph Batson (by invitation), Dr. John Shapiro (by invitation), and Dr. Harris Riley (by invitation), Nashville, Tenn.

Proliferation of reticuloendothelial elements is an outstanding pathological manifestation of such diseases as Niemann-Pick's, Gaucher's, Hand-Schüller-Christian's, Letterer-Siwe's, eosinophilic granuloma of bone, histoplasmosis, and tuberculosis. In several of the above, this represents a secondary response to more basic disorders. Acute disseminated reticuloendotheliosis (Letterer-Siwe's disease), together with Hand-Schüller-Christian's disease and eosinophilic granuloma of bone, constitute a triad of nonlipid disorders that primarily effect reticuloendothelial elements. Clinically and pathologically, intermediate forms of the three diseases are seen, but no attempt will be made to clarify this controversial interrelationship.

In presenting this paper, the authors are concerned only with acute disseminated reticuloendotheliosis, the rarest of the group. Approximately 41 cases have been reported previously; however, during the past 10 years 14 patients with this disease have been observed in Vanderbilt University Hospital. Every effort was made to include only those patients typical of acute infantile reticuloendotheliosis. Characteristic lesions were present at autopsy or biopsy with one exception, and the clinical features of this case were typical.

These 14 patients are presented in tables which summarize our experience with the disease and its course. Characteristic features of the illness were present, including maculopapular rash, fever, hepatosplenomegaly, hemorrhagic diathesis, lymphadenopathy, anemia, and bone lesions. Several of these are illustrated in photographs and photomicrographs. Although the disease is usually considered fatal, two of our patients are thought to be cured. The clinical course of these will be presented in more detail, and the possible effects of antibiotics, x-radiation, and splenectomy will be discussed.

It is apparent that acute disseminated reticuloendotheliosis is not an uncommon disease in this locality. In our experience its incidence is comparable to that of acute disseminated histoplasmosis, in which reticuloendothelial proliferation is also present. The striking clinical and pathological similarity of the two diseases is discussed.

DISCUSSION

Dr. Arthur F. Abt, Baltimore: My chief object in discussing this excellent presentation of Amos Christie and his colleagues is to emphasize the historical background. I have nothing to add to the etiology of the condition. Dr. Farber is here, and I am sure I do not wish to enter into any of the pathologic discussion.

In the presidential address of our society, given by Dr. McIntosh yesterday, he pointed out that one of the satisfactions of a medical career may be the grouping together of a symptom-complex, with the description of a syndrome which has no etiologic basis. I have probably been fortunate in being implicated in two such instances.

In 1924, when I was a resident at the hospital in Chicago, my classmate and colleague, William Bloom, was a resident in pathology, and he described and differentiated a group of cases similar in some respects to Gaucher's disease, but different, and he named this syndrome Niemann-Pick's disease. I was able to aid him in the clinical description of these cases, and also to describe with him the circulating Niemann-Pick cell.

Ten years later I came upon a very unusual case which puzzled me extremely, and in searching the literature and using the training that I had acquired, I decided to call this condition Letterer-Siwe's disease.

As Dr. Christie and his associates have pointed out, there are approximately 41 cases of this condition which have been reported, and 14 cases have been observed in Nashville. This is indeed a noteworthy observation. It might mean that Dr. Christie and his colleagues possess especially keen diagnostic acumen and recognize more of these patients with Letterer-Siwe's disease than the rest of us. Or perhaps, as he so well points out, there may be an epidemiologic relationship to the unusually large number of cases which they have had the privilege of observing.

Recently the occurrence of sarcoidosis has been epidemiologically linked with the rural areas in southern states, notably by Michaels, of Atlanta.

The reason I chose, in 1935, to name this condition after Letterer, who described the first case, and Siwe, who described the fifth case—our case being the ninth in the series—was that rather than give it a 38-plus-letter-word title, and I used a more extensive terminology in my title, I thought a proper-name title would be better.

In the era of the middle 1930's, reticuloendotheliosis was in the medical spotlight, much as gamma globulin is today. It was there chiefly because of the writings of a famous pathologist, L. Aschoff. I emphasized at that time under the term reticuloendotheliosis a wide variety of diseases were being reported and grouped, some of known and others of unknown etiology.

At that time, I could see no advantage either for clinical recognition, diagnosis, or for purposes of pathological classification, in grouping these cases under the so-called reticuloendotheliosis, a term which then, as now, seemed all-inclusive and meaningless.

It should be remembered that the term reticuloendotheliosis is derived from the fact that whenever a small or large part of the mesenchyme of the body has been found to react, this will ocur either in phagocytic or hemopoietic direction.

The connective tissue derives from the mesenchyme. As was stated, the most important function of the connective tissue seems to be its active role in various defense reactions.

As I originally pointed out, the same reticuloendothelial hyperplasia may be found in acute pyogenic diseases, the chronic granulomatous inflammations, neoplasms, certain leukemias and lymphogranulomas, and lipid storage diseases, as well as in eosinophilic granulomas, as Dr. Farber so ably pointed out.

Just a note as to histoplasmosis. It was brought to my attention in 1939 when a paper was published by Harry Agress and S. H. Gray, in which was noted a case of histoplasmosis with reticuloendothelial hyperplasia. Their case was one of generalized fungus infection (Darling's histoplasmosis). It was observed in an infant in St. Louis.

According to them, this was the second case reported in an infant and the seventh case reported in the western hemisphere of this condition. They noted reticuloendothelial hyperplasia locally in the arterioles of the lungs. This report is in agreement with the findings of reticuloendothelial hyperplasia reported by Dr. Christie in his cases of histoplasmosis.

When these diseases of known etiology or similar nature are separated out, there remains a group of cases originally described by Letterer, Siwe, and myself. Unfortunately still of unknown etiology, but hopefully, as the authors of this paper pointed out, they may at some time in the future be tied to some definite etiologic factor. Until such time, they are doomed to exist as a symptom-complex either under a many-lettered name or under the name of the authors who have attempted to group them into a clinical entity.

DR. SIDNEY FARBER, Boston: I should like to congratulate Dr. Christie and his colleagues on this very interesting and excellent presentation. I have had the opportunity of reading Dr. Christie's manuscript. First a word about the name.

My late teacher, Dr. Wolbach, always emphasized that names were given usually at the period of greatest ignorance concerning the nature of a disease, and this is no exception. The name which Dr. Christie suggests, acute disseminated reticuloendotheliosis, I would urge not be used for several reasons. In the first place, this is not an acute disease. It may go on for weeks, months, or years without specific therapy. It is disseminated. I like that part. But the word reticuloendotheliosis, I agree with Dr. Abt, would serve only to perpetuate what was an extremely useful and valuable designation 30 years ago, but which has long since outworn its usefulness. Dr. Christie showed us lymphocytes, plasma cells, mononuclear cells, and many other forms in the exudate. It is not justifiable to include all of these in the reticuloendothelial system.

So many different disorders have been described under that term that I think anyone reading it would have occasion to ask always, just what kind of disorder is meant in a particular instance.

There are some good reasons for using Letterer-Siwe's disease. The name is short, as Dr. Abt has pointed out, consisting of only 12 letters. And then Dr. Siwe is such a delightful person. When the nature or cause of this disorder is known, then this term for it should be dropped.

Now with regard to the nature of the disease. I am interested in the apparent concentration of the patients in Nashville. I don't believe that that has any etiologic implication at all. I think it merely means that Dr. Christie and his colleagues are interested in this disorder, that they are studying the patients very carefully, and that they are reporting them. We have had in the last seven years some 20 examples of this disorder in Boston. Most of them have come from New England.

When Dr. Walgren's splendid paper appeared, we found that we had arrived independently at the same conception, on the basis of our own studies during the 10 years before his report. In agreement with him, I think that it is impossible to differentiate clinically or pathologically between Letterer-Siwe's disease and Hand-Schüller-Christian's syndrome as a whole.

Now what can we learn from treatment if we cannot learn anything from specific biologic studies? As far as treatment is concerned, I should like to express my great interest in the fact that two patients have presumably been cured by the use of antibiotics, but might I emphasize, as Dr. Christie did, that this disorder may be complicated by secondary infection. There is also evidence that spontaneous improvement does occur, or improvement with very little treatment, in any one of the several members of this rather confusing group of disorders.

I would not withhold antibiotics at all in the treatment of these patients, because if one does, one will lose the patient earlier. But I would not expect to have an antibiotic actually bring about cures.

I would cite two cases which we have had in our own experience. We have a boy now of 15 years, who, as an infant, had this picture which Dr. Christie showed so clearly today with the scalp and the skin lesions, the bone marrow involvement, the draining ear, the lesions of the skull, mastoid, rib, scapula, femur, and ilium. That boy was treated with very small amounts of antibiotics. For his bone lesions he received a combination of small amounts of radiation and surgical removal of lesions in one or two instances. He is now alive and completely well at the age of 15 years.

We have another boy at the age of 7½ years, alive and quite well, with the same background.

Most of these patients die early. Their lesions may respond to antibiotics for a time or to corticotropin (ACTH), to cortisone, to triethylene melamine, to folic acid antagonists, and to other carcinolytic agents.

Finally, in conclusion, I am delighted with Dr. Christie's interest in this condition from the point of view of an infectious disease. We have attempted, as he has, to use the various methods available to clinical and laboratory workers today in an attempt to find some causative agent. We have looked here, as have numerous pathologists in the case of rheumatic fever, in the tissue for evidence of an actual agent that might be expected to be present in a lesion of this kind.

I might conclude by mentioning the studies which have been carried on by a number of people, including Dr. Alan Crocker now, and Dr. Laurence Kingsland. We found no evidence of any single etiologic agent. If we were to make a comparison, we would choose the exudative and proliferative aspects of rheumatic fever, or the protean manifestations of tuberculosis, particularly in those parts of the body where the lesions are not produced by the tubercle bacilli actually at the site of the lesion. It is of interest that 63 years ago Dr. Hand, of Philadelphia, described the beginnings of all of this as an infectious disease of unknown etiology, and I believe he made some comparison with tuberculosis.

DR. ALEX J. STEIGMAN, Louisville: My comment is anecdotal and is made to give support to the belief that the etiology of this condition may be multiple, with the clinical picture brought about by a unitary mechanism.

I refer to a 4-month-old infant who presented the clinical picture so clearly described by Dr. Christie, with a hemorrhagic, seborrheic, maculopapular eruption, a miserable infant with splenomegaly, whose skin eruption could in no way be distinguished from what we ordinarily regard as Letterer-Siwe's disease.

Closer inspection of the generalized eruption revealed three burrows, which looked surprisingly like scabies.

Removal of acari from a burrow was ample confirmation; treatment with benzyl benzoate was followed by prompt recovery. So much for the anecdote with a happy ending.

The actual biologic mechanics of scabies, which has not been widely written about, involves a good many things which are very interesting. I am largely indebted to Dr. Kenneth Mellanby for my information.

Scabetic infants' mothers have antiacarine antibodies which can be demonstrated in a number of ways. These are placentally transmitted, and following exogenous infestation postpartum, a hyperergic cutaneous response may develop in the next several months.

I do not make this comment to suggest that scabies is a common cause of Letterer-Siwe's disease, but rather to raise the question of whether the syndrome is a hyperallergic response to a number of individual agents. This is in keeping with the comment that Dr. Farber made about a generalized response to a variety of individual causes.

DR. MURRAY H. BASS, New York: I am very much interested in both the discussors and the doctor's paper.

Two years ago Dr. Horace Hodes, Dr. Samuel Sapin, and myself published a paper on reticuloendotheliosis, stressing the value of cortisone and corticotropin (ACTH) in its treatment, not as a cure but as a useful adjuvant. One of our cases, first seen at a year of age, presented bilateral discharging ears, a seborrheal eruption, splenomegaly, hepatomegaly, and what had been considered mastoiditis. X-ray of the skull showed multiple lesions characteristic of Hand-Schüller-Christian's disease.

The child was hospitalized and treated with antibiotics but did poorly. Cortisone was tried and resulted in return of appetite, disappearance of fever, and great general improvement. The child was discharged only to return very ill. The clinical picture she presented was now typical of the cases described by Dr. Christie today: papular and hemorrhagic rash, ear discharge, premature eruption of the teeth, hepatomegaly, splenomegaly, general adenopathy, multiple bone lesions, high fever, and extreme malnutrition. She appeared moribund, and as a last resort corticotropin was given intravenously for 10 days, resulting in a remarkable recovery.

Today, four years later, she again presents the typical picture of Hand-Schüller-Christian's disease and is a dwarf with proptosis, polydipsia, polyuria, and bone lesions. Contrary to most of the described cases, she has passed from the Letterer-Siwe syndrome to the Hand-Schüller-Christian syndrome, from the acute to the chronic stage of the disease. A history such as this would favor the theory that Letterer-Siwe and Hand-Schüller-Christian are stages of the same illness.

I was interested to hear that Dr. Christie had a case in siblings. I had one family with three children. Each of the three children died during the first year with typical Letterer-Siwe's syndrome.

DR. AMOS CHRISTIE, Nashville, Tenn.: I just want to take this opportunity to thank the discussors, particularly Dr. Farber and Dr. Abt, for their very illuminating discussion; as usual the discussion can be much better than the paper, and that is one of the reasons for getting these cases together.

I think it gives us inspiration to go back to Nashville and to whip up a little more enthusiasm in an attempt to find an etiologic technique, Dr. Farber, and to give it a better name. We surely tried. I notice that you didn't do very well yourself!

Conjugates of Adrenal Corticoids in Human Plasma. DR. ALFRED M. BONGIOVANNI (by invitation), DR. GEORGE W. CLAYTON (by invitation), DR. MELVIN M. GRUMBACH (by invitation), and DR. JUDSON J. VAN WYK (by invitation), Baltimore.

The understanding of the physiology and disease of the adrenal cortex has come to depend more and more on the estimation of levels of steroids in the blood rather than the amounts excreted in the urine. The procedure of Nelson and Samuels, which is widely employed in the determination of the blood corticoids, measures only the free (unconjugated) fraction. This portion of the steroids does not represent all of the material present in the circulation and hence may reflect only partially the status of adrenocortical function.

By the application of special methods to the study of human plasma, the conjugates of the steroids have been released, and it appears that considerably larger quantities of corticoids are present than heretofore reported. When the conjugated steroids are taken into account, the amounts present following the administration of Compound E are far greater than previously recognized, and several hours later the total levels are not so low as originally believed. This suggests that a significant proportion of circulating hormones remains unmeasured by current techniques.

The method involves the hydrolysis of human plasma with beta glucuronidase, dialysis, and extraction of the dialysate. The compounds so released were similar to pure Compound E in their absorption spectra following treatment with phenylhydrazine. Acid hydrolysis at pH 1.0 followed by dialysis was also used, but was found to be unsatisfactory.

These results call for a reevaluation of the levels of circulating corticoids in human blood. Normal values are about double those reported previously, since the conjugates represent about 50% of the total. By paper chromatography, both free Compound E and tetrahydro E were identified in in the free fraction and predominantly tetrahydro E in the conjugated fraction, after the administration of cortisone by mouth. In patients with cirrhosis, the compounds were poorly conjugated, and high free levels persisted longer. It appears that conjugation of corticoids is important in their normal disposition.

DISCUSSION

DR. ROBERT KLEIN, Pittsburgh: I want to congratulate Dr. Bongiovanni on this very important piece of work. At his suggestion last year, we began similar studies, although we used an acid method of hydrolysis. Most of our conclusions are indentical, and we will present them on Thursday. However, there are, I think, one or two points I should like to mention at the present time.

First of all, in renal disease, the conjugate level rises to extreme limits, whereas the free corticoid is at normal or low level.

There is also apparently some difference in the rate of conjugation between adults and children. Children conjugate and perhaps also metabolize the corticoid more slowly. I don't know at the moment what the significance of this is, but it may explain some of the differences in free corticoid levels that have been previously described.

We have reached a somewhat different conclusion as to the importance of these materials. We at the moment feel that they are products ready for excretion and have no great significance within the body and that the free corticoid still represents the proper measurement of stress, and so forth.

DR. LYTT GARDNER, Syarcuse, N. Y.: I want to congratulate Dr. Bongiovanni on this excellent piece of work. We have recently been investigating the plasma transport of 17-ketosteroids utilizing fractions prepared by the methods of Prof. E. J. Cohn and associates. Fractions IV (especially IV-4) and V were found to contain the highest concentrations of 17-ketosteroids on analysis (*Bull. Johns Hopkins Hosp.* **94**:105, 1954). This raises the possibility that the mode of transport of the 17-ketosteroids in plasma is as the "lipo" of the alpha-lipoproteins.

I am curious to know if Dr. Bongiovanni has had an opportunity to see if he can locate these bound corticoids in one of the Cohn plasma fractions.

DR. ROBERT S. ELY, Salt Lake City: I should like to ask Dr. Bongiovanni what his speculations are on the possible role of these conjugated steroid forms in adrenal hormone metabolism and if he has found especially high levels of the conjugate in certain clinical cases, in contrast to the ratio he finds in the normal patients.

I should also like to ask a question on the methodology; does he feel that the dialysis procedure in the beta glucuronidase extraction technique is a necessary part of the conjugate measurement? I saw that the Cushings cases that Dr. Bongiovanni showed did not have a very high level, and I only want to mention that this has been in contrast with the findings that we have had in Cushings cases. Why this disagreement exists, I don't know.

Also, what significance does he think the slower rise in the serum levels of the conjugate formed in contrast to the free steroid has, other than the obvious one of liver metabolism?

And finally, the statement made regarding Dr. Sweat's fluorometric procedure for separating Compounds F and E; Dr. Bongiovanni said that he found, unfortunately, that these hormones

could not be separated. I think this is a very practical statement. However, using the micro-silica gel column, Dr. Sweat has been able to separate E from B and F, although I think he is the only one so far who has been able to do it with this technique.

Dr. Vincent Kelley, Salt Lake City: We recently have been doing decay curves on injected Compound F, and I think there are some interesting correlations here.

Maybe it isn't surprising, but it isn't what we expected—that in those patients who, in general, have low steroid levels, such as the rheumatic patient with well-established rheumatic fever, the rate of fall of the Compound F level in the blood is very slow, as compared to the normal rate, approximately double the amount of time being required to reach a zero level.

Incidentally, in any patient, when one puts Compound F into the blood in such quantity that initial levels of 100 γ per 100 cc. develop, one can expect that the steroid level will fall off to a zero value. If this is plotted on a semilogarithmic scale, a straight line plot is obtained. Comparing the slopes of the semilogarithmic plots provides a nice technique for determining the comparative rates of removal of steroids from the circulation.

We know that the steroids removed from the circulation don't appear in the urine in quantities sufficient to explain the amount removed, and we think conjugation of the steroids probably is involved in this removal. Incidentally, in the patients with liver disease who have high circulating free steroid levels and, as Dr. Bongiovanni has just showed, low conjugated levels, the rate of disappearance of injected steroid from the circulation is very slow, as compared with normals.

Dr. Alfred M. Bongiovanni, Baltimore: I am not suggesting that the conjugates are active or not active. Schneider's work has definitely shown that the material we find in the conjugated fraction is a metabolite of the active form that preceded it. I think it is worth once more stressing that even in the free fraction, not all of the material is active, since on paper it has been found the inactive derivatives may be present.

I want to thank Dr. Gardner for his comments. I cannot answer his question. We haven't looked into the matter. As you know, we don't use any procedure which would digest protein, such as Dr. Gardner has found it necessary to use for the 17-ketosteroids. But then they are apart from the corticoids, and I am sorry I cannot give him any more information.

In answer to Dr. Ely's question on dialysis, I discussed this with Don Nelson a couple of weeks ago. I don't think dialysis is absolutely necessary if one washes the abstract in one form or another. I have been hesitant too, because of losses with such small quantities of material, but that may well work and I think should be tried. This is really a preliminary report, as I said at the outset. Not all of our Cushings are low. The ones shown here are low, and of course one of the two we showed was high on another day.

Frequently, in studying Cushings, we are not certain of the diagnosis.

As for the other point of Dr. Ely's, the fluormetric separation of E and F, I didn't mean to imply that we couldn't separate E and F. The point is that direct communication from Dr. Sweat indicates that Compound E does not fluoresce. Therefore, you wouldn't use fluorescence in quantitating Compound E.

I wish to thank Dr. Kelley for his comments about the slow rate of fall in the free state and liver disease; certainly that seems to have been our experience.

Testicular Feminization in Presumably Normal "Girls." Dr. William C. Deamer, San Francisco.

There is a syndrome which is often familial and which is characterized by a completely feminine psyche and figure—including mature breast development—in persons having absence of the uterus, scant or absent pubic and axillary hair, a short vagina, and male gonads. There is no abnormality of the adrenal glands, and no ovarian tissue is present. The testes may be located in the pelvis in the position usually occupied by the ovaries or, as is often the case, they may be associated with an inquinal hernia.

The histology of the gonads is usually typical of that found in cryptorchid testes—with considerable interstitial cell hyperplasia. Evidence suggests these cells as the site of estrogen production. The few urinary hormone studies done have usually given values in or near the normal range for children before puberty and for women after puberty. In one adult instance of the syndrome, Wilkins has reported that administration of androgen failed to cause any evidence of masculinization, the end-organ response apparently being "female-directed."

Although well over 100 such cases have been reported, one finds almost no mention of it in the pediatric literature, and the syndrome is not generally known. The presence of a mass, usually thought to be an ovary, in a bilateral or unilateral hernia is what would usually bring the patient to the doctor's attention before puberty, whereas amenorrhea is an additional cause for investigation after puberty.

The genetic history suggests a strong familial and hereditary tendency, with transmission only through the normal women in the family. Several generations are often affected.

Four instances of the syndrome have recently been studied at the University of California Hospital and are reported. Three of the four are in siblings aged 9, 5, and 1½ years. In addition to showing the usual testicular type of gonad, skin biopsy in one of our cases showed the male type of chromatin masses in the nuclei of the epithelial cells.

DISCUSSION

DR. WILLIAM A. REILLY, San Francisco: I think that Dr. Deamer is to be commended on two scores. First, for bringing this to the attention of pediatricians, for there are very few of these cases described in pediatric literature, and second, even though Dr. Deamer has not had enough time to work up these cases more thoroughly, they are excellently presented to us.

Here is another endocrine syndrome, genetically conditioned; this gives us a new thought about endocrinology. We have already known, for instance, in what Fuller Albright described as ovarian dwarfism, with agenesis of the ovary, that subsequently the dwarfism was not related to the ovarian deficit, and that it was thought to be genetically conditioned.

Here Dr. Deamer has presented evidence of another genetically conditioned endocrine disturbance.

DR. HORACE L. HODES, New York: I should like to add an experience with the biopsy technique which Dr. Deamer mentioned. In a case of a child who was a hermaphrodite, the skin biopsy settled the question. The sections clearly showed the large XX chromosome mass, indicating that the child was a girl.

Dr. Deamer didn't have time to go into it, but if one looks at the sections, it is quite easy to see the difference between the XY and XX chromosome masses. The lantern slide did not do the technique justice. The XX chromosome combination is large enough to see in the cells of the female, while in the male the XY combination is too small to see.

DR. JOHN A. BIGLER, Highland Park, Ill.: This report is quite disturbing to me, because it does not tell the true sex of a patient with pseudohermaphroditism, and this report would indicate it is difficult to tell the true sex of a patient where testes are present.

We have recently had a patient very similar to the one reported tonight, with a large phallus and with what we thought was hypospadias; exploration revealed the presence of fallopian tubes, no uterus, no vagina, but testes. In addition, this patient was quite dwarfed and also had diabetes for a period of six years.

On the basis of the biopsy, which showed testes, we went ahead and assumed that the patient was a male, and plastic procedures have been done on the external genitalia, so he now appears as a male, and it is rather disturbing to me to think of the possibility that in the next year or two he is going to develop secondary characteristics of a female.

I wonder if Dr. Deamer would have any suggestion as to how to distinguish what is going to happen to these patients before adolescence.

DR. MELVIN M. GRUMBACH, Baltimore: I am very sorry that Dr. Wilkins is not here to comment on this interesting paper. Over the past 15 years, Dr. Wilkins has seen about 40 patients with intersexuality of the type unassociated with adrenal hyperplasia.

The largest portion of this group has been male pseudohermaphrodites. By this term we mean persons with a mixture of various degrees of male and female differentiation of the genital system but with gonads consisting only of testicular tissue. We do not believe that one can predict with certainty how these testes will function hormonally at puberty. If the external genitalia completely simulate the female type, as in Dr. Deamer's patients, it is only the rare few who will not feminize at puberty. One such patient seen recently had a normal female distribution of sexual hair. Another, previously studied by Dr. Wilkins, did not have any sexual hair, despite the presence of rudimentary hair follicles microscopically in the skin over the pubis. Large doses of androgen did not produce any growth of sexual hair, clitoral enlargement, or

deepening of the voice. This indicated an insensitivity of the end-organ to androgen. The associated genetic defect of lack of sexual hair has also been seen in an otherwise normally developed fertile woman.

In another group of male pseudohermaphrodites with enlarged phallus, urogenital sinus, and cryptorchidism, it is impossible to predict whether the testes will produce virilization or feminization at puberty.

Dr. Joan Hampson and Dr. John Money, of the Department of Psychiatry, have been comprehensively investigating the psychological development of our group of hermaphrodites. Their studies have indicated with very few exceptions that hermaphroditic persons belong psychologically and psychosexually to the sex of their rearing, irrespective of chromosomal, gonadal, and hormonal sex, and despite ambiguous external genitalia. It is extremely desirable to decide the sex of rearing, once and for all, before the end of the first year of life. The decision should not be deferred until puberty. After a child has learned and established his or her gender it is psychologically dangerous to impose a change of sex during childhood, and with rare exceptions should be avoided. With the patient first seen after adolescence, greater latitude is permissible deferring in large part to the person's wishes.

DR. EDNA SOBEL, Boston: Dr. Deamer has mentioned that his patients failed to respond to androgen, as did the person described by Dr. Wilkins. These observations strongly suggest that the tissues themselves are not sensitive to androgen, whether endogenous or exogenous.

I wonder whether the whole syndrome may not be a failure of end-organ response to androgen beginning in embryonic life. In rabbits, at least, the presence of embryonic testes is necessary for the differentiation of the male reproductive tract. In France, Jost has demonstrated that the removal of the testes of the fetal rabbit before the reproductive tract has begun to differentiate leads to persistence of the Mullerian system, so that uterus and tubes are formed, while the Wolfian system regresses. In the absence of the fetal ovary, feminine differentiation progresses normally. Failure of the tissues to respond to fetal testicular hormones from the beginning of life might account for the development of a female reproductive tract in the presence of fairly normal testes. In this case the syndrome would represent a failure of response on a cellular level, rather than a primary endocrine disorder.

DR. LYTT GARDNER, Syracuse, N. Y.: I don't think we should confuse the chemical status of the patient with the sex of the patient, in the everyday use of the word "sex." I say this seriously, since one is apt to be influenced by statements concerning the excretion of 17-ketosteroids, or the excretion of estrogen, or ratios between the two, and one might be tempted to relate this to the sex of the patient.

Actually, we see urinary excretions of 70, or 80, or 100 mg. per day of 17-ketosteroids in a female pseudohermaphrodite with congenital adrenal hyperplasia, untreated, who may be a perfectly feminine attractive girl.

We may see the same finding in a genetically female pseudohermaphrodite—a perfectly healthy "boy"—who has been raised as a "boy" through diagnostic error. But I think that we must dissociate any isolated psychological test, cytological test, or chemical test from influencing the final decision as to what sex the patient should exist as in society.

This problem has been recently reemphasized by our experience with a child with congenital adrenal hyperplasia, a female pseudohermaphrodite, who was recognized in the newborn nursery to have abnormal genitalia and who was correctly raised as a girl for five years. At that time, the diagnosis was reversed, in the sense that she was raised as a boy until the age of 13 years.

Then at the age of 13 years, we saw this child, who was excreting large amounts of 17-ketosteroids, and was a very active "boy." The child was examined exhaustively by Dr. Joan Hampson and Dr. John Money, of the Department of Psychiatry at Johns Hopkins, who have made a special study of these problems. It was their opinion that this child must continue to be a boy, since the antecedent environmental conditions were such as to make hazardous any chemical reorientation of the patient's sex at this late date. For this reason, the child was not feminized with cortisone or hydrocortisone therapy. So this is a very complicated medical situation which really requires, I would say in all instances, the collaboration of an understanding psychiatrist, and if possible a psychiatrist with special experience in this field.

DR. WILLIAM C. DEAMER, San Francisco: I want to thank all the discussants, whose comments I found most interesting, and I heartily agree with the last speaker, or those speakers

who implied that the determination, either by skin biopsy or by gonadal biopsy, of the sex of the patient should not necessarily determine the path to be followed in advising the parents and in guiding that person in the future.

Whether the three girls I have belong to that syndrome which I talked about or not, certainly those persons who have attained that type of maturity can only be women. Most of them are married. Most of them are quite happily married, and I think many of them have no idea that there is anything histologically wrong with their gonads. I say "histologically wrong," because that is about the only thing that is wrong with the gonad. It seems to be, in their case, producing estrogen which serves all their purposes quite adequately. Since they have no uterus, the fact that the gonad doesn't overproduce doesn't handicap them additionally.

But I think while I didn't comment on it, I am glad one of the discussants did. The subject of Dr. Wilkins' demonstration in one case, that of the 30-year-old married woman whose picture I showed you, was incapable of an androgenic response. He applied testosterone ointment first to the hair follicles of the pubic area, and then gave considerable doses of testosterone systemically, and she had no evidence of being capable of masculinization in any way at all. That person was more female in that respect than the normal woman, who responds to such approach with masculinization.

So these people can only be women. Whether my patients belong to that group or not I leave for you to decide. I believe they do.

One of the discussants mentioned a case in which he was uncertain, in view of this report, as to how he should look at that case. One helpful thing to do would be to determine whether the uterus or cervix, or both, are present in that person, because the presence of the cervix, I would say, takes the person out of the syndrome as presently described, as does also a hypospadias phallus.

We may be able to test the effect of estrogen in the 9-year-old girl, and the concept is that perhaps the whole trouble is end-organ insensitivity to androgen, and therefore the androgen normally present in the male takes over and develops the organs.

The amount of estrogen and androgen in the few well-studied cases would indicate that there is a little more than that to the story and that the amounts of estrogen and androgen resemble those of the female, as I say, in a few well-studied cases, more than they do the male.

But I think that question of end-organ responsiveness needs further investigation, and possibly we can use our patients for a test of that fascinating response some time in the future.

Effects of Splenectomy in Mediterranean Anemia, with Special Reference to Fetal Hemoglobin Synthesis. Dr. Carl H. Smith, Dr. Irving Schulman (by invitation), Dr. Richard E. Ando (by invitation), and Dr. Gertrude S. Stern (by invitation), New York.

Quantitative determinations of fetal hemoglobin serve as an index of endogenous hemoglobin synthesis in severe Mediterranean anemia. Nine patients with severe Mediterranean anemia and two with combined Mediterranean anemia—sickle-cell disease—ranging in age from 4 to 18 years, were intensively studied during their postoperative course. Observations included transfusion requirements, clinical changes, and the effect upon fetal hemoglobin synthesis.

While the fundamental defect is intracorpuscular, the hemolytic or extracorpuscular component associated with hyperactivity of the spleen usually supervenes to aggravate the anemia. The survival of transfused normal erythrocytes determined in the preoperative and postoperative periods in random patients confirmed recent studies demonstrating their shortened life-span in those with splenomegaly and normal survival in those with splenectomy.

Following splenectomy, hemoglobin levels are not restored to normal, but tend, nevertheless, to be maintained at higher levels with fewer transfusions. That this elevation represents an actual increase in total circulating hemoglobin was demonstrated by preoperative and postoperative hemoglobin mass determination. In one of the patients, no further blood supplements have been required for two years. It is our impression that better results appear in general in the older patient.

Marked and continued subjective improvement was uniformly noted, except for the return in certain patients of severe skeletal pain. The fact that relief was obtained by transfusion despite the absence of severe anemia may be ascribed to the postoperative resumption of maximal erythro-

poiesis within the bone marrow. The relative freedom from this symptom prior to operation suggests that this effort was minimized by periodic blood supplements and suppression of endogenous blood formation.

Confirmatory of this hypothesis were the cyclic changes in fetal hemoglobin incident to blood transfusion. The fact that severe Mediterranean anemia represents the only pathological state in which fetal hemoglobin occurs in extraordinary amounts, suggested the value of quantitative estimations of this component in the presplenectomy and postsplenectomy periods, to determine the possible effect of transfusion on its synthesis.

With the aid of blood volume estimations, it was possible to convert the percentage of hemoglobin to total circulating hemoglobin mass. In the postsplenectomy period, the fetal hemoglobin increased spontaneously, only to be depressed by subsequent measured blood supplements. Comparison of the fetal hemoglobin mass before and after transfusion demonstrated unequivocally that this effect could not be attributed to dilution with donor blood, but represented a specific depression of endogenous fetal hemoglobin synthesis. Expansion of the fetal hemoglobin mass depended not so much on removal of the spleen, as on the decrease in transfusions which the operation afforded.

These studies demonstrate that quantitative determinations of fetal hemoglobin serve as an index of endogenous hemoglobin synthesis in severe Mediterranean anemia, that maximum values are achieved when transfusions are reduced or terminated following splenectomy, and that certain clinical symptoms may be correlated with its fluctuations. It remains still to be determined in what manner priority of fetal over adult hemoglobin synthesis is integrated with the pathogenesis of severe Mediterranean anemia.

DISCUSSION

DR. HUGH WILSON JOSEPHS, Baltimore: In Baltimore, recently, we splenectomized twins. The immediate improvement in one was great enough to lead the mother to insist on the same operation for the other child.

One of them is still living, and although not cured, is able to maintain an adequate hemoglobin level with greatly decreased numbers of transfusions. The other one, however, after a first improvement, went on and died of hemochromatosis.

Now I mention these cases because I wonder about Dr. Smith's experience with hemochromatosis in this disease, and the possibility that in taking out the spleen one has removed an organ which ordinarily stores iron in harmless form, so that it is more available for storage elsewhere in situations where it can act in a toxic manner.

DR. RUSTIN MCINTOSH, New York: I wonder if Dr. Smith, with his wide experience in hypoplastic anemia, could state whether the suppression of endogenous blood formation occurs only in conditions such as sickle-cell anemia and Mediterranean anemia, in which the bone marrow turnover rate is so greatly increased, or whether a similar phenomenon also occurs in hypoplastic anemias.

DR. IRVING J. WOLMAN, Philadelphia: Two observations merit a little more discussion. One is the matter of the spleen appearing to cause excessive destruction of the red cells. The phenomenon is pretty clearly demonstrated in the reported cases. One cannot say that it is a universal phenomenon. Nevertheless, one might expect that at least some of the cases would also have leucocytopenia, or a low platelet count, or both, and that following the operation, these levels would return to normal.

A great many clinics are in the habit of taking out the spleens in this disease during the infancy period for mechanical reasons because of the large size of the organ. The youngster is thereby relieved of carrying that weight.

With respect to the bone marrow inactivity, or depression, or whatever name one chooses to give to the phenomenon, it does appear, so that after transfusion the red cell production is slowed down a little bit. At least that appears to be the natural inference from this very fine study on the fetal hemoglobin. One wonders, however, whether transfusions should therefore be kept to an absolute minimum. One could argue that the induction of a transitory rest period within the bone marrow, which is functioning at a very rapid level of red cell production, may not be a good thing for the child in the long run.

DR. WOLF W. ZUELZER, Detroit: I don't want to belabor the point too much, because both Dr. Kaplan and Dr. Wolman have made it, but I can enlarge on it to this extent.

That in clearly congenital hemolytic anemias, especially those of duration, the occurrence of superimposed acquired mechanisms immune or otherwise is by no means rare, and when Dr. Kaplan was in Detroit, we followed a whole series of such patients.

I think that while the observations are very important, both therapeutically and theoretically, we ought to stress the fact that this may be entirely nonspecific and not part of the Mediterranean syndrome as such.

DR. CARL H. SMITH, New York: I believe, Dr. Josephs, your reference is to the identical Greek twins who had originally been patients at the New York Hospital and were reported by Govan subsequently. Splenectomy in these children at 5 to 6 years of age resulted in alleviation of their condition insofar as fewer transfusions were needed to maintain a level of 5 gm. of hemoglobin. It is still to be demonstrated whether stabilization at this low level is desirable in rapidly growing children.

The suggestion that the spleen acts as a reservoir for iron derived from transfusions and therefore serves to prevent its spread to the liver and pancreas is an intriguing one. While this relationship may exist to a certain extent, several observations concerning the role of the spleen in iron metabolism discount its importance in this direction. It has been shown by Finch that following a transfusion, although the spleen receives a large increment of red cells, internal distribution of iron immediately takes place to other organs. An increasing number of observations have also emphasized that in refractory anemias an associated defect in the regulation of iron absorption occurs. Excessive amounts of iron may be absorbed from the gastrointestinal tract to appear in parenchymatous organs as well as the spleen, regardless of excessive iron stores from transfusion therapy. Thus in one of the patients not included in this series, transfusions accounted for 6 gm., while at postmortem examination the liver disclosed 27 gm., of iron. It should be pointed out that excessive tissue iron, namely, hemosiderosis, originating from multiple transfusions does not invariably lead to hemochromatosis. Other as yet undisclosed factors are involved in this change, although chronic hypoxia has been regarded as important in causation.

With respect to Dr. Kaplan's previously reported cases showing normal survival rates in Mediterranean anemia, I believe our observations explain the discrepancies by demonstrating a decreasing life span of tranfused cells with increasing age of the patient, so that in general a normal life span is expected in an infant and a sharply decreased survival in the older child and adult. The two cases of Kaplan and Zuelzer, aged 2 and 7 years, respectively, were probably milder than usual, since their cases showed a normal serum iron and considerable iron-binding capacity. In our experience, the severe case of Mediterranean anemia receiving only a moderate number of transfusions shows an elevated serum iron and absent iron-binding capacity.

In answer to the question as to the fate of the person whose spleen is not removed, this depends on the level at which the hemoglobin is stabilized. It is based on the capacity of the bone marrow to adjust itself to the demands of abnormal hemolysis. In the 30-year-old patient whose decreased red cell survival was shown, a severe burn precipitated a drop in the hemoglobin level which despite transfusions could no longer rise spontaneously to previously maintained levels without splenectomy.

In our experience, severer skeletal pain occurs in certain patients with Cooley's anemia whether or not the spleen has been removed. The fact that it can be relieved by transfusions, especially postoperatively, has suggested to us that this may be due to overactivity of the bone marrow when the person depends exclusively on his own blood formation.

I did not mean to give the impression that the suppressive effects on hemoglobin synthesis and erythropoiesis developed exclusively in Mediterranean anemia. Inhibition can take place to some extent in other refractory anemias, especially when multiple transfusions are given.

I agree with Dr. Zuelzer that the extracorpuscular defect does not occur solely in severe Cooley's anemia. When a spleen receives the impact of multiple transfusions over a prolonged period, especially in hemolytic disease, an extracorpuscular defect may become manifest. This has been demonstrated by Janet Watson in sickle-cell anemia in cases with splenomegaly.

The extracorpuscular defect should be separated from hypersplenism, as Dr. Wolman implies. The occasional occurrence of leucopenia and thrombocytopenia before splenectomy and the large numbers of nucleated red cells following this procedure may be regarded as manifestations of

hypersplenism. An adequate plan for transfusion therapy in Cooley's anemia and other refractory anemias still has to be evolved. We attempt to maintain our children at hemoglobin levels of 7 to 7.5 gm. unless symptoms set in at higher levels.

Finally, in clinics with large numbers of cases of severe Cooley's anemia, the consideration of splenectomy is inevitable, and the evidence we have presented emphasizes its advantages in the older patient. I wish again to emphasize that removing the spleen does not influence, as far as we know, the basic intracorpuscular defect of this disease.

Hematopoietic and Goitrogenic Effects of Cobaltous Chloride in Patients with Sickle-Cell Anemia. Dr. Ruth T. Gross (by invitation), Dr. Joseph P. Kriss (by invitation), and Dr. Theodore H. Spaet (by invitation), San Francisco.

An enteric-coated preparation of cobaltous chloride has been used in the treatment of patients with sickle-cell anemia. Four children and one adult have been followed for several months with observations before, during, and after therapy. Studies with filter-paper electrophoresis have shown no demonstrable effect of cobalt on the abnormal migration of hemoglobin in these patients. Each of these patients, while receiving cobalt, achieved a hematopoietic response involving hemoglobin, red blood cells, and hematocrit, which was greater than any of the spontaneous fluctuations which occurred during the pretreatment period. In the treatment of the four children, the dose of cobalt was progressively increased in order to achieve a maximum response, and in each instance the blood values rose, reached a plateau, and then decreased. Two children receiving 3 mg. per kilogram of body weight per day of the cobalt preparation developed visible goiters which, on biopsy, proved to be thyroid hyperplasia. In one of these, clinical signs of myxedema and laboratory findings of hypothyroidism were present. In the other, the laboratory determinations were suggestive of hypothyroidism. A third patient, who had thyroid function studies done prior to the institution of cobalt therapy, developed a goiter and marked reduction in radioiodine uptake which could be correlated with the rise in the serum cobalt level. In each case the clinical and laboratory findings of thyroid inhibition reverted to normal when therapy was discontinued.

A period of six weeks to two months at a dose of 2½ to 3 mg. per kilogram per day appears to have been crucial in the development of goiters with this preparation of cobaltous chloride. At the time that the goiter appeared in each patient, the hemoglobin had fallen below the pretreatment level.

Administration of placebo tablets covered with the same enteric coating had no effect on thyroid function or hematopoiesis.

Administration of a second preparation of cobaltous chloride supplied by a different manufacturer and with a different coating produced a significant reduction in radioiodine uptake in one patient within three weeks and in another patient within five weeks.

These studies indicate that cobaltous chloride is a goitrogenic agent. The fall in hemoglobin which followed the initial hematopoietic response may be related to the superimposition of hypothyroidism.

DISCUSSION

Dr. Angus G. McBryde, Durham, N. C.: We have recently given a cobalt-iron preparation (Roncovite), 0.3 cc. daily, to 10 premature infants whose birth weights were from 1,100 to 1,500 gm. This preparation was given from 2 to 8 weeks of age; one of these infants at the end of 6 weeks developed a diffuse enlargement of the thyroid gland. This subsided within two weeks after discontinuing Roncovite. Hemoglobin levels on the group receiving Roncovite were similar to those of premature infants of the same weight who received iron alone.

Dr. Irving Schulman, New York: The hematologic changes presented in this paper were in terms of concentration measurements.

I wonder whether any studies were made of blood volume and total circulating hemoglobin before, during, and after cobalt. This seems important to me for three reasons: first, because of the remarks concerning the inconstant reticulocyte changes, second, because these patients developed endocrine manifestations which may be associated with fluid shifts, third, because in studying cases of sickle-cell anemia we found that rises and falls in hemoglobin concentration could occur as a result of plasma shifts alone, while the actual total circulating hemoglobin remained unchanged. In some instances of crisis the hemoglobin concentration (in grams per

100 ml. of blood) rose while the total circulating hemoglobin fell. The rise in hemoglobin concentration was, therefore, the result of plasma volume shift rather than the result of blood production.

DR. CHARLES D. COOK, Boston: I should like to ask Dr. Gross if one should infer from this very excellent presentation that cobalt plus thyroid may be useful in treating patients with sickle-cell anemia?

DR. WILLIAM A. REILLY, San Francisco: This is very reminiscent of goitrous cretinism first reported by me to the Society for Pediatric Research in 1940, with observations of high iodine uptake. I should like to ask Dr. Gross if she has any explanation for the mechanism of this paradoxical situation.

As I recall her data, one patient had increased uptake of I^{131}. Several others did not; all had hyperplasia of the thyroid gland.

Does Dr. Gross feel that this is due to increased T.S.H. production, or does she have another mechanism in mind?

DR. ROLAND B. SCOTT, Washington, D. C.: I should like to ask Dr. Gross if she will give us a brief statement as to what she considers justifiable criteria for the therapeutic use of either cobaltous chloride or blood transfusion in children with sickle-cell anemia, particularly since the cobalt may be potentially harmful.

DR. LYTT GARDNER, Syracuse, N. Y.: I should like to compliment Dr. Gross on an excellent and meticulous clinical study, the likes of which we would like to see more of.

This is the sort of study which gives useful data to the preclinical people. I think it is nice for the distribution of knowledge to go in that direction occasionally.

DR. RUTH T. GROSS, San Francisco: Dr. McBryde, although the manufacturers have stated that there have been no goiters noted with the use of Roncovite, your experience would indicate otherwise, and I am most interested to hear about it.

Dr. Schulman, I am sorry we did not do total circulating hemoglobin, and I can only say that I am in complete agreement with you that these studies would have been benefited by such determinations.

Dr. Cook, we are at the moment giving thyroid to one of our children who is still on cobalt and who does now have a goiter and also a very low hemoglobin, lower than he had at the start of treatment. I don't know what has happened to that child.

Dr. Reilly, I think I did not make myself clear at one point. The increased radioiodine uptake in one child occurred after cobalt was stopped. It was first normal, then low during cobalt therapy, then went up to 47, and at five months it was back to normal. All of our children did have decreased iodine uptake.

Dr. Scott has asked for the criteria for the use of transfusions or cobalt. I could perhaps answer this best by reminding you of the patient whose data were on the slide, the one who had received 32 transfusions. This was the patient on whom we started cobalt therapy. The reason that we started cobalt therapy was because we had just done a survival time of the donor cells which had been given to that child and the survival time was six days.

This child had been bedridden for one year and could no longer be transfused. We felt absolutely desperate and thought we would try cobalt. I cannot now tell you any indications for the use of cobalt. At the moment I do not feel that it is a safe drug. I would feel happier if we learned more about this drug before we used it, particularly in patients with anemia.

I should like to conclude by thanking Dr. Gardner for his very kind remarks.

Inhibition of Brain Respiration in Vitro by Bilirubin: Reversal of Inhibition by Various Means. DR. RICHARD L. DAY, Brooklyn.

Bilirubin was tested for its effect on the oxygen uptake of chopped rat brain. Rats weighing from 30 to 100 gm. were decapitated. The brains were removed, cut into small pieces with scissors, and placed in Warburg flasks at 25 C. The fluid bathing the tissue was either a slightly alkaline electrolyte solution or a similar electrolyte solution containing bilirubin in concentrations ranging from 5 to 100 mg. per 100 cc. Control and experimental solutions were adjusted so as to be similar in acidity and osmolarity. With bilirubin concentrations above about 0.02%, oxygen uptake was depressed about 25%. The inhibition could be reversed by oxidation of the bilirubin

to biliverdin and by the action of cytochrome C and methylene blue. Bilirubin purified by crystallization behaved similarly. Preliminary observations with serums from normal and jaundiced infants yielded results similar to those with commercial bilirubin.

The results are summarized in the Table.

DISCUSSION

DR. ARLISS H. TUTTLE, Memphis: It would be interesting to know if you have determined whether or not there is deposition of this pigment within the cells of the brain preparation during the experiment.

DR. WILLIAM J. WATERS, Syracuse, N. Y.: I should like to compliment Dr. Day on this fine piece of work, and I think perhaps it may well add another important link to the concept of bilirubin encephalopathy. I should like to say that recently we have been able to get some newborn rats jaundiced with staining of the brain by intraperitoneal injection of a bilirubin solution. I should like to ask, therefore, whether in these experiments he has had any experience with newborn brains.

I think perhaps the time period here may be critical, and I notice that the weights of the animals as given were between 25 and 75 gm. Most of the newborn rats that we worked with weighed approximately 10 gm., and therefore I am wondering about the age of these animals. In the rats over 10 days of age we were able to get some of these jaundiced using a similar technique as with the newborn rats, but were unable to obtain any staining of the brain.

Oxygen Uptake of Chopped Rat Brain in Various Media, Expressed in Microliters per Milligram per Hour (Wet Weight)

Additions to Medium	No. of Observations	Mean ± St. Dev.	Significance of Difference from Control	Significance of Difference from Bilirubin
None—control	22	0.663 ± 0.065	.....	.....
Bilirubin	31	0.490 ± 0.066	$p < 0.001$	.....
Biliverdin	9	0.623 ± 0.085	$p > 0.05$ (Not sig.)	$p < 0.01$
Bilirubin plus cytochrome C	8	0.689 ± 0.094	$p = 0.5$ (Not sig.)	.....
Cytochrome C	8	0.733 ± 0.048	$p < 0.05$	$p < 0.01$
Bilirubin plus methylene blue	6	0.680 ± 0.106	.....	$p < 0.01$

In relation to Dr. Tuttle's question, in terms of humans at least, by microspectrophotometric techniques, we are able to say that the pigment within the cells in newborn infants dying with brain damage from hemolytic disease of the newborn is bilirubin.

DR. FRED H. ALLEN JR., Boston: Dr. Najjar proposed some time ago a theoretical explanation of how bilirubin could be a toxic agent, showing that it was very much like heme in structure. He proposed that perhaps bilirubin may compete with heme for the protein moiety on cytochrome molecules and thus interfere with respiration. Dr. Day's work is further suggestion that this may be so.

I should like to ask Dr. Day whether he has any idea that giving methylene blue or cytochrome C to seriously jaundiced infants might be a logical thing to do.

He is entirely correct in warning us not to let any prejudices we may have about the cause of kernicterus have too strong a hold on us. Those of us who use bilirubin tests as guides in exchange transfusion therapy know that by and large they are very reliable. At the same time, we all have to admit that we really don't know the cause of kernicterus.

DR. SAMUEL P. BESSMAN, Washington, D. C.: I am very interested in this work that we have presented here on the bilirubin effect on respiration. I should like to know whether Dr. Day has studied the effects of other metals in the system and what effect bilirubin has upon such metals as magnesium and, particularly, copper, which have been implicated in the transport of oxygen to cytochrome C.

One can predict from its structure that bilirubin might form strong chelates with the heavy metals.

DR. RICHARD L. DAY, Brooklyn: Dr. Tuttle, the cells after contact with bilirubin looked yellow, but I don't know whether the bilirubin was on the surface or inside.

Rats whose blood bilirubin has been raised to levels of 70 to 80 mg. or more give a very nice picture of kernicterus in the gross, but on microscopic examination, the cells don't look yellow, so I have to assume that the gross appearance is not indicative of true kernicterus. These rats die during convulsions.

Dr. Waters, the reason we took small rats was because with our rat colony this was the cheapest way to get uniform material. We did make some preliminary observations to see whether use of 25- or 200-gm. rats made any difference. It didn't seem to.

There is no question—and it has been in the literature for many years—that brains of immature animals pick up circulating pigments like trypan blue very much more easily than older brains, and there is also no possible doubt that the blood brain barrier is a very real thing and is low in immature animals. Just how this fits in with kernicterus is not clear to me, though a good case can be constructed favoring the participation of a lowered barrier.

About the possible action of bilirubin, Dr. Allen, because of its structure, the difference between biliverdin and bilirubin makes interpretation confusing. There is not much difference in their structure, and yet biliverdin does not have much inhibitory action.

I would be the last person to suggest any therapy on the basis of this work. I must, in fact, warn against the use of methylene blue, because if it causes any kind of precipitate in the animal similar to the one in the test tube, it might be harmful. Cytochrome C, I am sure, would be harmless if sterile, and I have to confess that we have given it to some rats, but are not ready to report on the results.

Dr. Bessman, we tried iron at the suggestion of Dr. Shemin, but I don't want to state the results, because they might be in error.

Early and Reliable Guide in the Prognosis and Management of Hemolytic Disease of the Newborn. DR. THOMAS R. BOGGS JR. (by invitation), and DR. NEVA M. ABELSON, Philadelphia.

Appraisal of the severity of hemolytic disease of the newborn in a given infant and decision as to the need to perform initial and repeat exchange transfusions have been based on multiple factors such as maternal history, maternal Rh antibody titer, hematologic findings, serial serum bilirubin levels, physical findings, and state of maturity of the infant.

Frequently the resolution of these multiple considerations into an evaluation of the infant's disease consistent with the initial findings and subsequent clinical course is difficult. This is true particularly among those physicians who have not had a great deal of experience in the field.

Repeated serum bilirubin determinations have been of great help in simplifying the problem but frequently fail to provide an adequate index, particularly in the first 12 hours of life.

Examinations of the absorption patterns of the plasma pigments of these infants by a simple spectrophotometric technique provide a quick and reliable evaluation of the babies' immediate and future status.

Our experience in the management of infants with hemolytic disease during the past 18 months, according to this technique, will be presented.

DISCUSSION

DR. RICHARD L. DAY, Brooklyn: I should like to ask Dr. Boggs if he has made measurements of these pigments in hemolytic anemias in older subjects. We still have the mystery of why kernicterus seems to be confined to the newborn period.

I should like to mention a thought that has come to me. Dr. Herbert C. Miller has shown a paradoxical response on the part of newborn infants to hypoxia. Instead of breathing more, to compensate, their ventilation diminishes. One wonders if some action by these pigments opposing respiration might set off this vicious cycle and thus explain in part why this pigment or some other pigment or other factors operate harmfully only in the newborn period. This is pure speculation, of course.

DR. ARLISS H. TUTTLE, Memphis: I think the correlation between spectrophotometric studies and the clinical studies is excellent. There is one point I should like to make, and that is that the measurement of absorption at 415 mμ would not necessarily include a measurement of the peak of absorption of all the heme pigments.

Hematin itself, in buffer solution, has a rather diffuse peak, from about 385 to 395 mμ I believe; methemalbumin, or pseudomethemoglobin, which is probably the state of the hematin as it exists in the circulating serum, has a rather sharp absorption peak at 405 or 406, as shown by Rosenfeld and others. I wonder if this possible discrepancy should be taken into consideration in attempting to measure total heme pigments.

I should also like to know what precautions were taken to avoid hemolysis during withdrawal of the blood samples. Dr. Kaplan, Dr. Najjar, and several other have mentioned that it is practically impossible to withdraw venous blood from the newborn infant and avoid significant hemolysis. This has also been our experience.

DR. EDITH L. POTTER, Chicago: It is very well known that after the first exchange transfusion, bilirubin levels are entirely without value, and I should like to know whether it has been found that for the original exchange, as determined by bilirubin or by heme levels on cord blood or blood taken in the first few minutes after birth, the feeling is that this constitutes an adequate means of deciding whether or not exchange transfusion should be done.

DR. FRED H. ALLEN JR., Boston: I should like to ask Dr. Boggs what his results were with babies who were brought into the hospital at less than 2 hours of age. Was he able invariably to control the pigment levels in any group of babies, in particular those whom he saw early?

DR. A. ASHLEY WEECH, Cincinnati: I wish Dr. Boggs would clarify in my mind the absorption curve of bilirubin itself and whether or not it isn't still absorbing down at 415. I haven't got a clear picture, because I know the peak of bilirubin is a higher figure than that, but they are both down in the 400's, and I wonder whether bilirubin is excluded entirely.

DR. THOMAS R. BOGGS JR., Philadelphia: First I should like to thank the discussers for their very nice comments.

In answer to Dr. Day's question as to whether we have observed these pigments in other hemolytic anemias, I should like to state that we have. We have seen high 415 peaks in a case of acute acquired hemolytic anemia and in a case of moth ball poisoning or naphthalene injestion. We have also seen high 415 peaks in cases of hemolytic disease of the newborn due to ABO blood group incompatibilities and in a case of severe hemolytic disease of unknown etiology in a newborn infant who at age 9 months appears to have Cooley's anemia. To date, however, we have only seen evidence of alkaline hematin or methemalbumin in toxic cases of hemolytic disease of the newborn due to an Rh incompatibility. These substances peak at 405 to 410 mμ whereas oxyhemoglobin peaks at 415 mμ.

I quite agree with Dr. Tuttle's comment as to the 415 peak. It has been our experience also, that there is a peak for methemalbumin between 405 and 410.

I can answer the question in reference to the introduction of oxyhemoglobin by hemolysis secondary to the trauma of a venepuncture by showing you a slide. We have been interested in this problem also. As a result, I took a speciment of blood from an infant who was a very sick baby with hemolytic disease and in whom we knew there was alkaline hematin present. This specimen was divided into two portions. One portion was handled according to our usual routine. The other portion was subjected to trauma by being pushed through a small No. 23 needle with force four times. This trauma, which was very excessive, did cause a considerable increase in the amount of total pigment measured spectrophotometrically, but did not cause any increase in the amount of alkaline hematin present.

In answer to Dr. Potter's question, yes.

In answer to Dr. Allen's question, also yes.

Dr. Weech inquired as to whether the height of the 460 peak influenced the height of the 415 peak and vice versa. The answer is yes, and we have worked out formulae to correct for this effect. The formulae are as follows:

$$\text{The net or absolute value at } 415 = \left(\text{O.D. } 415\ \text{m}\mu - \frac{\text{O.D. at } 460\ \text{m}\mu}{2}\right) 1.1$$

$$\text{The net or absolute value at } 460 = \text{O.D. } 460\ \text{m}\mu - \frac{\text{O.D } 415\ \text{m}\mu}{5}$$

The total serum bilirubin can be determined by multiplying the net value at 460 by 1,000 k. The constant k is a calibration factor and our standards give us a k value of 0.052.

In answer to Dr. Miller's first question, we have not seen significant amounts of heme pigment in normal infants. As to Dr. Miller's second question of whether one can control the heme pigments if the infants are treated early enough, the answer is most of the time, yes, but sometimes no. If not, there is a higher incidence of failures.

Three Unusual Cases of Anemia of the Newborn. Dr. Bruce Chown, Winnipeg, Man., Canada.

Three cases of anemia in the newborn will be reported, two nonhemolytic and one hemolytic with a probable nonhemolytic factor. In one, serological and biochemical evidence proves that the baby had given its mother a large intrauterine transfusion, or series of transfusions, possibly extending over a period of two or three months before delivery. In one, a gross placental defect, combined with vaginal bleeding early in the labor and shock in the baby, suggested a late transplacental hemorrhage. In the third, what was believed to be a transplacental transfusion from baby to mother led to what appeared to be a transfusion reaction in the mother and a fatal hemorrhagic state in the baby.

DISCUSSION

Dr. Robert Cooke, New Haven, Conn.: Dr. Chown's paper is very interesting. I think we all have problems in the newborn in trying to diagnose nonhemolytic anemias. The infants very fortunately have tagged red cells, and I wonder if the use of the simple quantitative determination of fetal hemoglobin might help in solving some of these problems. Perhaps the determination of the fetal hemoglobin in the mother might be of use in deciding how much blood from the baby has gotten into the mother's circulation.

Also the quantitative determination of fetal hemoglobin on the bleeding from the uterine cavity might also help in deciding what percentage of blood has come from the mother and what has come from the baby.

Perhaps this type of determination might solve some of these problems in the future.

Dr. Clement A. Smith, Boston: I think this is something that we have all seen more often than we know. I notice there is a paper reporting a number of similar cases in the program of the Society for Pediatric Research. We saw it most dramatically, I think, in a baby where the bleeding occurred from the placenta after the baby and the placenta were born.

A few years ago, a paper appeared which purported to show that infants delivered by Caesarian section are in shock because they receive less placental blood than those normally born, and advising that the baby and the placenta should be kept as a unit after Caesarian section until the baby had received whatever might drain into it from the placenta.

This resulted in a number of babies arriving in our nurseries with the placenta attached. Soon after this procedure became current, one of these babies was observed to be very pale an hour or two after its birth. The placental basin was filling with blood which the baby was obviously losing through a defect in the placenta.

Adjustment of plasma volume must normally occur within a couple of hours after birth, to judge by the studies of Windle and others on blood volume and hematocrit of infants retrieving placental blood.

Dr. Chown has shown us in this paper that, conversely, anemia may increase extremely rapidly if red cells have been lost before or during birth and plasma is then increased to keep the blood volume constant within a very short time after birth.

Dr. A. Ashley Weech, Cincinnati: I want to thank Dr. Chown very much for his presentation. About 18 months ago, I received a letter from a former resident, then in the Army of the United States and doing obstetrics as well as pediatrics, Dr. Hugo Smith. Smith had delivered a baby after a rather protracted labor, and when the head appeared, the cord was pressed around the head, and the baby subsequently was found to be quite anemic. He wrote me and asked if I thought it was possible that this circumstance had led to the baby bleeding into the mother's placenta.

I did not know, but I wonder if Dr. Chown would not agree that his was a plausible theory.

Dr. Carl H. Smith, New York: We have recently reported a group of cases with the designation of "Nonhemolytic Anemia of the Newborn" that resemble those presented by Dr. Chown. The group we have described includes infants in whom anemia of moderate severity was noted either at birth or within the first few days of life and who showed no jaundice or

erythroblastemia. The factors of incompatibility of blood groups, overt hemorrhage, hemolysis, and infection were excluded as causative factors, and the outcome has been uniformly favorable. It is possible that these cases correspond to certain ones listed as anemia of the newborn in the era before the discovery of the Rh factor and their assimilation into the hemolytic disease syndrome. We postulated for our group a prematurely developed hypoplastic state which normally has its onset later on in the postnatal adjustment period. The conspicuous infarcts permitting the loss of fetal blood in Dr. Chown's cases were not present in ours. Furthermore, our group showed diminished reticulocytes in contrast to increased numbers expected in hemorrhage. However, it is important in future cases to search for placental sites of occult blood loss, which Wiener has suggested as a cause of neonatal anemia. Knowledge as to what extent neonatal anemias may be based on placental defects awaits the type of investigation Dr. Chown has so well presented.

DR. FRED H. ALLEN JR., Boston: I think the thing that Dr. Chown should be congratulated for most is the beautiful simplicity with which he demonstrated fetal blood in the mother's circulation. Certainly, the test for fetal hemoglobin is the easiest to do and as a quantitative test is by far the most accurate.

Ordinarily, there would be some red cell incompatibility between fetus and mother, which could also be tested, and I think it was a little unusual that in his case there was only the Rh incompatibility.

There is one group, however, in which such demonstration would usually be impossible. Twenty per cent of babies are compatible with their mothers in the ABO blood group. In this situation, one would be unable to show fetal cells in the maternal circulation, unless a large number had just gotten in, because the mother would very rapidly destroy incompatible red cells. Even the fetal hemoglobin test would fail.

I should like to ask Dr. Chown one question that bears on a question that he asked, and unfortunately no one has answered, and I suppose no one can. Would he tell us, please, how many nucleated red cells were present in the circulation of, I think it was, the second baby. The number of nucleated red cells frequently becomes in the minds of most people a very important differential point between hemolytic disease and other conditions that may cause anemia. If this baby had, for example, 200 or 300 nucleated red cells per 100 whites, I think that is an extremely important thing that we would like to know about.

DR. JAMES F. BOSMA, Salt Lake City: I think we have a variance of the circumstance—nonhemolytic anemia of the newborn—that we have observed in a pair of twins.

These twins were born at an outlying hospital in Utah. One of them was subsequently brought to a hospital in Salt Lake City, and I had an opportunity to see it. The story is incomplete.

I should like to mention that in this clinical circumstance, one of the twins was born with a hemoglobin of 4 gm. per 100 cc., and the other with a hemoglobin of 31 gm. The one with the marked hyperemia subsequently developed hyperbilirubinemia and went on to kernicterus, in which state it has subsequently survived. We would think that speculatively this may have been an example of autotransfusion between two twins. Presumably this autotransfusion had occurred at the time of labor or some time before that.

DR. ARTHUR F. ABT, Baltimore: As long as we seem to be unwinding it—separating out the hemolytic and the nonhemolytic anemias, I wonder into what category hydrops fetalis falls? Is it due to an anomaly of the placenta?

DR. EDITH L. POTTER, Chicago: Dr. Chown, I think, has done a very nice job in following up the idea that we have all had that there must be some way of proving what we all assume to be true, and I think that he has two excellent examples here. One in actually demonstrating fetal cells in the maternal circulation, and the other in demonstrating a chill in the mother that could very well be due to the abrupt introduction in her circulation of fetal cells.

Years ago, when we were all still anxious to prove the Rh as responsible for hemolytic disease, before we had the albumin method of testing for antibodies, we at one time gave 25 cc. of Rh-positive blood to an Rh-negative woman who had delivered an immunized baby, which was followed by a rise in temperature, a chill, mild jaundice, and an increase in bilirubin in the blood. So that we know that the introduction of Rh-positive blood at least into an immunized patient can produce such a reaction.

I think, however, that one must be extremely careful in attempting to prove by observations in the placenta that one has had actual introduction of the fetal blood into the maternal circulation. I believe that it occurs, but at one time I looked a some 10,000 consecutive placentas and cut sections of all of them, and we see constantly many placentas; holes, so-called, in the placenta, and breaks in the maternal surface, which is decidua, are extremely common.

One has to remember, too, that the circulation through the placenta is between the villi. Maternal blood is constantly circulating between the individual villi, and according to most investigators in the field at the moment, the drainage of the placenta is from the marginal sinus at the periphery. Dr. Chown said he couldn't find a hole by which this blood was getting out of the original area in the first place. One would not expect to be able to see any outlet, because the blood moves between the villi toward the periphery of the placenta.

However, when you realize that maternal blood is constantly in movement in these areas, there is no reason to suppose that fetal blood being intermixed, escaping into this flowing of circulation, wouldn't move with it, and the fact that one sees an open space between villi and the placenta is surely no proof that this hole should be considered to have been able to hold 50 or 70 cc. of blood—my only feeling would be that it must be an artifact. We see it so constantly, and unless all maternal circulation through the placenta stopped, there is no reason why the fetal blood would not be carried on with the maternal blood.

A second thing is that a break in the surface of the placenta is in the decidua, which is a maternal portion. The surface of the uterus comes away with the placenta, and there again one would expect any break in the decidua and a separation of the villi to not produce any changes that could be considered an indication of fetal hemorrhage. I am not intimating that fetal blood may not escape into the maternal circulation, but no one has as yet devised a way of proving from the placenta that it is this that occurs.

Dr. Bruce Chown, Winnipeg, Man., Canada: I agree with Dr. Cook that the determination of fetal hemoglobin is probably a good method of proving whether or not the fetus has bled into the mother's circulation, unless, as Dr. Allen has pointed out, the fetal cells are destroyed by maternal antibody, so any method, chemical or other, will fail. I have an idea that by very careful differential agglutination, one can prove smaller quantities than you can by chemical methods. I am not a chemist.

In reference to restoration of plasma volume after hemorrhage, I don't know that because plasma volume is reduced rapidly after birth it necessarily follows that it will be increased with equal rapidity. Dr. Weech suggested 15 minutes in the experimental animal; maybe it can be as fast as that in newborn babies; it's an interesting problem.

I apologize to Carl Smith. Although I know his paper well, I didn't know he had coined the good term "nonhemolytic anemia of the newborn." I agree with him; there must be other types of nonhemolytic anemia. All I have done is illustrate two hitherto unproved types.

There was no nucleated red cell count done on the first baby, Dr. Allen; "a large number" was reported. In the second one, there was a count, and as I recall, it ran about 5,000 per cubic millimeter.

We didn't get early counts to know whether a rise in reticulocytes preceded other evidence of anemia or not.

I agree with Dr. Abt that we need to reassess the problem of hydrops. We have seen several cases in which there has been no blood incompatibility and no congenital anomaly; in such cases the prognosis is good for normal babies in later pregnancies.

With reference to Dr. Potter's discussion, as little as 3 cc. of Rh-positive blood injected into a sensitized person can produce a transfusion reaction. So it could be quite a small amount that, crossing the placenta, might cause a reaction if the passage of the blood were rapid.

In the first case, as I understood Dr. Potter to say, she thought the placental "lesion" probably an artifact. It may well be, but I should like to restate our argument. The mother had symptoms suggesting partial separation. She passed excess blood in the third stage. She did not become anemic; the baby did. The excess blood was probably fetal. Fetal blood could not be demonstrated in the maternal circulation by serological or chemical methods. The placenta was abnormal, part atrophic, part hypertrophic. In the most hypertrophic cotyledon was the cavity I have shown you. We could not discover any other bleeding point in the fresh placenta or cord, nor could Dr.

Hertig's laboratory in the fixed specimen. We therefore believe that the cavity is not an artifact but the site of severe fetal bleeding. Dr. Hertig will not commit himself, and we certainly cannot prove our belief beyond all doubt.

Extrapyramidal Cerebral Palsy with Hearing Loss Following Hemolytic Disease. Dr. Randolph K. Byers, Dr. Richmond S. Paine (by invitation), and Dr. Bronson Crothers, Boston.

Patients with extrapyramidal-type cerebral palsies following hemolytic disease of the newborn constitute a distinct clinical entity separable from the over-all group of cerebral palsied. Undoubtedly, many infants recognized as having severe kernicterus in the neonatal period die at this time, and others die early in infancy. Nevertheless, an appreciable number survive to later childhood and adulthood, and other such cases are discovered in which kernicterus was not initially recognized. The present report includes 20 patients with cerebral palsies believed due to neonatal hemolytic disease, who are part of a larger group of roughly 400 cerebral palsy patients in a follow-up study. Fourteen of the 17 surviving patients are over 5 years of age, and 7 are over 12 years.

Eleven of the 17 have moderate or severe motor handicaps, all of these being cerebral palsies of the extrapyramidal type, including most conspicuously limpness, extreme incoordination, persistent immature postural patterns, such as tonic neck patterns and neck-righting reflexes and retarded motor development in infancy, and athetosis in later childhood. Only 1 patient fails to show some degree of athetosis in the entire group of 17. None of the patients show spastic cerebral palsies, although seven have minor pyramidal tract signs. Sixteen of the patients walk independently; 15 of these began to walk under 5 years, but the other patient not until 10 years. The gait is useful in all, and in general the degree of motor deficit is less than one would expect from earlier reports.

Eight of the patients have severe hearing loss, up to 100 decibels and uniformly more pronounced in higher frequencies. Four show a milder but significant hearing loss. None are proved to hear normally, but in five there is complete disagreement between clinical and parental impressions of deafness and normal psychogalvanometric skin resistance responses; it is possible that a higher level of perception than the cochelar nuclei may be involved. The existence of hearing loss was uniformly recognized by parents earlier than by physicians, and failure to detect it was frequently the cause of unjustified diagnoses of mental deficiency and of delay in education. Two patients showed deafness with insignificant motor handicaps in the form of very mild athetosis.

The degree of intellectual, as well as motor, deficit was less than had been anticipated. Testing of intelligence is often extremely difficult in this group of patients, but of 14 patients satisfactorily tested, 7 had normal intelligence and 4 others, I.Q.'s above 70.

Another characteristic of cerebral palsies due to hemolytic disease, in addition to hearing loss, may be a poorly understood dyskinesia of ocular movements, involving chiefly vertical gaze, which tends to be accomplished by movements of the head rather than the eyes.

Motion pictures will be shown of a young infant with typical kernicterus and of older patients of the type described.

While all but 1 of the 20 patients had recognized (or easily recognizable in retrospect, in the case of those now adults) hemolytic disease, only 2 had clinically recognized kernicterus in the neonatal period.

Testing of the patients' and mothers' bloods was done at follow-up in all instances and disclosed Rh incompatibility in 16 (of 18) and incompatibility of Group A in the other 2. All but one of the mothers with Rh incompatibility still had anti-Rh titers of 1:8 or more, and in one instance as high as 1:64 after an interval of 22 years. Such testing would seem to be of value as a retrospective diagnostic criterion. Of the two mothers with A-incompatibility, one had an anti-A titer of 1:16,384, the other of only 1:1, but titers are probably of much less diagnostic value in this group.

DISCUSSION

Dr. Randolph K. Byers, Boston: There are just a few points that I would like to amplify in this presentation, and I made some notes as we went along.

In the first place, it seemed to me that these children, from the point of view of the emotional impact on the parents, can be divided pretty well into two groups. First, the group of children

in whom the disease occurred before the understanding of the usefulness of treatment in the newborn period. It makes a great difference as to whether the baby falls in this group or into the group who were not recognized and treated after this business was known.

The first parents at least can be talked into the point of view of having regret about the situation and maybe think they should have been older when they had children. The second group of parents are extremely bitter. Two sets of these parents, whom I know quite intimately, are very anxious to have men appear in court and present evidence of malpractice against the doctors who took care of them, and this point of view colors their attitude toward the children, and so on.

The parents' attitude toward the children, I think, is a thing of a great deal of importance in relation to how well they do.

The last child reported was the only child of a mother who was very anxious that this child do well and who worked and worked over the child.

She had physiotherapy in the most well-organized manner, at least as well as we know how to organize it, from the time she was born until she was about 8½ years of age or so, at which point we quit. She began to walk very soon afterwards.

We have seen that two or three times; children whose noses are being pushed onto the grindstone, in pursuit of something they are unable to do will quit on you, whereas if you let them alone and let them find their own way of doing things, even though it may be very physiologically different from what you and I do, will often get along pretty well with an apparatus that seems quite inadequate to the rest of us.

I think the group of children that we have seen contains several in whom the neurological evidence of kernicterus was not noted in the newborn period, and I recently saw another child whom we did not have time to include in the report seen in our hospital by various consultants, all of whom wrote notes on it saying that the baby did not have kernicterus, with eye defects quite like these.

That child was observed carefully. It isn't always true that we have as careful observation as that, but I think that this disease can turn up in children who show such minimal neurological signs in the newborn period that they can be missed. I think those are the main points that I wanted to bring out in relation to this situation.

We have not modified the motor activity of these children by any method of physiotherapy training and teaching, and our experience with them has been that if we try to give them experience in feel, in vision, in hearing, in all the other sensory fields which are usual to the runabout, that they become much happier and much more able children. If this is done, the difficulties of getting in communication with them are much less, and we find that many of the children whom we thought of as being quite dull at 2 and 3 years, when their deafness was not recognized and when their motor handicaps made them untestable, are quite intelligent people and able to learn a good many things and to have a good many interests in the world.

Dr. Frederick C. Moll, Seattle: This problem of delayed speech and hearing loss is problaby related and quite characteristic in these children that we see. I should like to ask the doctor what his experience is on the hearing aid introduced quite early in infancy, and one of the criteria would seem to me that pretty nearly every child with kernicterus should have a hearing aid from birth.

What do you suggest in that matter?

Dr. Fred H. Allen Jr., Boston: Dr. Paine and Dr. Byers are emphasizing the point that the diagnosis of kernicterus has often been missed in the neonatal period. I think it even more important, at the present time, to state strongly that there is no excuse for missing the diagnosis of kernicterus in the neonatal period.

Dr. Vaughan taught us in 1947 how to recognize kernicterus in the early neonatal period, and in the seven years since then there has not been a single case at the Children's Hospital, nor at the Boston Lying-in Hospital, in which kernicterus, confirmed at a later age, was missed during the first week. I know Dr. Paine will confirm this. In other words, if abnormal neurologic signs are completely absent during the first week of life it is proper to tell the parents flatly that the child will have no neurologic residuum of hemolytic disease. In fact, it is grossly unfair to the parents and the child not to do so.

I would go a little farther than that myself and say that if an infant with hemolytic disease recovers from the acute phase of its illness without ever having opisthotonos, he has not had

kernicterus and will not have neurologic residua; the parents should be so informed, in no uncertain terms. I feel so strongly about this because I know that the parents almost invariably need such assurance and need it badly. I think a great deal of harm would be done if pediatricians were to adopt a pessimistic "wait and see" attitude in all cases of hemolytic disease.

I should like also to express my gratitude to Dr. Crothers, Dr. Paine, and Dr. Byers for the careful follow-up study they are doing. The data they are gathering on the late stages of kernicterus are of very great value.

DR. MURRAY H. BASS, New York: I was very much interested in Dr. Byer's paper, especially because of a severe case of hemolytic disease of the newborn which I have been able to follow for 19 years. This patient was the result of the third pregnancy, the first producing a normal baby, the second, a stillbirth. On the first day of life the baby showed splenomegaly, hepatomegaly, deep jaundice, and severe anemia. She received several transfusions from the father with no signs of improvement, so that the father himself suggested another donor saying his blood was "no good." At that time the Rh factor had not yet been discovered. Blood from another donor resulted in rapid improvement. Unknowingly we had chosen an Rh-negative donor. Years later the family's blood grouping showed the father and child Rh positive, the mother negative.

The patient was left with severe neurological symptoms: muscular incoordination and athetosis, markedly poor development of gait and speech. In early childhood she appeared mentally retarded. Fortunately, her parents were wealthy and she had every possible advantage in the way of treatment by a psychologist, a speech therapist, and a physiotherapist, who gave her daily treatments during her entire childhood. She has improved enormously. She went through a period of depression at the age of 15, realizing her condition. She is now 19, has just completed her freshman year in one of the biggest girl's colleges in the country, and is a happy normal person. It just goes to show what can be done with some of these children that look hopelessly ill.

DR. HERMAN YANNET, Southbury, Conn.: Our experience with this type of cerebral palsy has been necessarily confined to the more seriously retarded. About 10% of our cases have been female and the rest male.

I was rather struck by the fact that most of the children and patients shown in the film have been girls. I wonder if this is just a casting technique, or whether we can have a breakdown of the sexes of Dr. Byers' group.

DR. RICHMOND S. PAINE, Boston: To answer first Dr. Moll's question about the hearing aids, the hearing loss as I mentioned is of varying degrees of severity. Not all patients will require a hearing aid, even eventually. Many of them, the milder ones, will teach themselves to lip read and will get along perfectly satisfactorily on lip reading alone. Others will require a hearing aid, but the age at which it can be fitted is an individual question which has to be answered for an individual child. The degree of motor disorganization, the degree of difficulty in keeping the erect posture, and the degree of emotional and mental disturbance in individual children all determine the age at which they can be fitted with hearing aids.

With a very young child, hearing aids costing what they do, it is usually a poor investment in that respect, and I don't believe there is any clear evidence that great damage results from delaying a hearing aid, even if it means delayed speech beyond the usual age of onset.

There are many children of the age of 4 or 5 years, and possibly even 3 years, who can wear a hearing aid with benefit. In the long run, I think the question is answered by whether the hearing aid gives sufficient benefit to the individual child to make sense to him. If it doesn't, he will discard it and not wear it.

To answer Dr. Allen's question, there is only one patient that I am sure of in our present series who was seen at the Children's Medical Center from the beginning and who later turned out to have kernicterus and a cerebral palsy and hearing loss, not so recognized in the newborn period.

The child was followed in the hematology clinic as a routine measure to determine the outcome of hemolytic disease patients, and was seen by several different observers, all of whom commented that there was no evidence of kernicterus.

A few patients with kernicterus had convulsions in the newborn period. None of our present series of patients have had convulsions since then. That is in keeping with extrapyramidal cerebral palsy in general, in which the percentage incidence of convulsions is no greater than in the random population.

Dr. Bass's history of the 19-year-old follow-up is an extremely interesting sociologic one. None of the patients whose motion pictures we showed this morning have been followed for that length of time, but we have a number of other extrapyramidal cerebral palsy patients, some of them having had hemolytic disease, who have reached adult life. We have also had the impression, as regards satisfactory emotional adjustments, that the girls do better than the boys. There is no greater assistance than great personal charm and parental wealth.

The leading girls' schools, like Vassar and Smith, seem more inclined to accept a patient with a handicap than some of the more ruthlessly competitive state institutions.

A depression of some sort in adolescence, when the patient becomes finally aware that the physical handicap is not going to disappear, is almost inevitable in most of these patients. Many of them overcome it with skillful guidance. It seems to come about particularly at that age, not only because the patient is more aware of his environment and of the ways in which he is different from other people, but also because his condition, which while it is pathetic, appealing, and cute in a small child, becomes grotesque and uncouth in a teen-ager.

With regard to Dr. Yannet's question, I don't have the figure here of the sex tabulation, but it is approximately 50/50. There are just as many girls as boys, and the selection of the motion pictures was purely coincidental.

Field Study of Retrolental Fibroplasia in Maryland. Dr. Hildegard I. M. Rothmund (by invitation), Dr. Paul Harper, and Rowland V. Rider, Sc.D. (by invitation), Baltimore.

A field study of the incidence of retrolental fibroplasia has been made as part of an investigation of all 4,700 premature infants born in Maryland in 1952. A staff physician saw all 160 prematures with a birth weight under 1,500 gm. who survived more than six months and were Maryland residents. Information was obtained by questionnaire either directly from the mother or through public health nurses for the 563 surviving babies in the 1,500 to 2,000 gm. group who were Maryland residents; the staff physician then visited those babies for whom the reply indicated any abnormality of the eyes.

All babies who had any detectable defect of vision were then seen by a small group of ophthalmologists for funduscopic examination under a mydriatic. Anesthesia was used when necessary to obtain a satisfactory view of the fundus. The standard classification adopted by the Joint National Committee on Retrolental Fibroplasia was used.

The data indicate that the proportion with residual lesions of retrolental fibroplasia is at least 5.5% among survivors whose birth weight was under 2,000 gm. This is between three and four times as great as the proportion found in the only other similar report in the literature (*Pediatrics* **11**:238, 1953). About one-half of the cases found had some useful vision in the better eye. The proportion with residual lesions within each weight group was highest in those infants with the shortest periods of gestation. The data suggest that the disease was from two to three times more frequent in babies cared for in the 5 top-ranking hospials (ranked as to conformity to standards of premature care) than in the other 41 hospitals. A positive correlation was found between the proportion of infants with residual lesions and the length of incubator care.

Growth Failure and Congenital Malformations Associated with Experimental Porphyria in Chick Embryos. Dr. Robert A. Aldrich (by invitation), Ellen L. Talman, Ph.D. (by invitation), Robert F. Labbé, Ph.D. (by invitation), James D. Case, M.S. (by invitation), and Richard A. Nevé, M.S. (by invitation), Portland, Ore.

Oral administration of Sedormid (allylisopropylacetylcarbamide) to mature rabbits and rats induces clinical and chemical changes resembling human "hepatic" porphyria (Schmid and Schwartz, *Proc. Soc. Exper. Biol. & Med.* **81**:68, 1952; Case, Aldrich, and Nevé, *ibid.* **83**:566, 1953).

White Leghorn embryonated hen's eggs were inoculated with 10 mg. of Sedormid in isotonic glycerine containing 0.1% sorethytan (20) monooleate (Tween 80) into the yolk sac on the

eighth day of life. Equal numbers of controls were prepared. Groups of treated and control eggs were sacrificed daily for nine days and their allantoic fluids pooled for chemical analysis. Red fluorescence in ultraviolet light characterstic of porphyrin was observed in fluid from treated eggs in 24 hours. Coproporphyrin and uroporphyrin were isolated and identified. The isomeric configuration of each porphyrin was at least 90% Type III. Porphobilinogen was not a constant finding but could be demonstrated qualitatively on several occasions. Liver catalase activity was markedly reduced in the Sedormid-treated chicks.

Dissection of the embryos under ultraviolet light showed bright red fluorescence of the mesonephrons and later the metanephrons when they became functional, all calcification centers of bone, and, in a few instances, the liver. The fluorescence increased tremendously while under the ultraviolet light, suggesting that more porphyrin was being formed during the period of observation. These observations indicate that Sedormid produces changes in the chick embryo which are identical to those seen in experimental porphyria of rabbits and rats and also resembles human hepatic porphyria (Talman, Frisch, and Aldrich, *Fed. Proc.* **13**:309, 1954).

It is of interest that in the chick embryo preparation the drug exerts its effects in the absence of bacteria, but this does not exclude the possibility that some of the effects of Sedormid-porphyria in laboratory animals may result from action of the drug on intestinal flora.

Chicks given injections of Sedormid often have difficulty extricating themselves from their shells when they hatch. When the chicks are hatched the weight of the treated birds is significantly less than the controls. In addition, a striking congenital malformation of the feet is observed in many of the treated birds but is not apparent in controls. Sedormid-treated chicks with foot deformities develop a high mortality rate between the third and fifth day after hatching. They seem no different in their behavior than others who survive, but suddenly become ill and die within a few hours. The foot deformity is different from the entity known as "slipped tendon disease," or fowl perosis. The toes are curled medially and the chicks seem weak in the upper leg as well, causing them to walk in a squat position. The tendon is not slipped off the hock. There is an associated malformation of the beak, and the birds are poorly feathered. All of the observers agree that the Sedormid-treated chicks seem unsteady, as if their sense of equilibrium is disturbed, and at times these birds show tremors.

Comparison of growth curves of treated chicks with controls maintained in the same brooder demonstrates a growth failure in the former. Sedormid-treated chicks do not catch up to the controls even after 30 days. The growth arrest can be shown to have started in the embryos soon after inoculation of the drug.

This is the first demonstration of growth failure or congenital anomalies associated with this particular disturbance of porphyrin metabolism. The nature of these changes suggests that other metabolic pathways and mechanisms may be involved in this experimental disorder. It is of particular interest that a probable common precursor for the synthesis of pyrrole and purine has recently been suggested (*J. Am. Chem. Soc.* **75**:4873, 1953). Data illustrating these statements from a study of more than 350 chick embryos will be presented. Further morphological and biochemical investigations of this phenomenon are in progress.

DISCUSSION

DR. DAVID YI-YUNG HSIA, Boston: This is a very beautiful piece of work which in some ways suggests that the changes in porphyrin metabolism are an indication of the toxic effects of certain agents upon intermediate metabolism which we do not as yet understand very well.

In association with this, I think it might be worth while to mention some observations regarding similar changes in lead poisoning. Dr. Byers and I have had the opportunity of observing the porphyrin metabolism in both the urine and the blood of patients with lead poisoning and found in both cases that the coproporphyrin measurements very closely reflect the degree of involvement. They can be used as a relatively rapid way of studying lead poisoning, both diagnostically and in terms of therapy, and I think the authors should be congratulated on bringing up another very important point.

DR. MILTON RAPOPORT, Philadelphia: I am sure Dr. Aldrich didn't say that the anatomical defects in growth retardation were cause and effect, that they were purely existing side by side.

The reason I say this is that some years ago Mitchell Rubin and I, doing experimental lead poisoning with rats, found that very small ones were excreting coproporphyrin Type 3 in magnitudes as great as 2,000 μ per day. For size, that was a considerable excretion.

At that time, Remington pointed out that there were excretions of similar and at times greater magnitude with sulfanilamide.

We speculated about the contribution to the changes of lead poisoning produced by coproporphyrin. I think you are entirely out on a limb. Those rats are retarded in growth, and I don't know how you can incriminate these things as cause and effect or as stemming from a common injurious agent.

DR. EDITH L. POTTER, Chicago: I should like very much to know whether there were any histologically demonstrable changes in the kidneys of these chick embryos which survived for a period of time.

DR. ROBERT A. ALDRICH, Portland, Ore.: All of these experiments were done using equal numbers of controls. These controls were raised in the same incubators under identical conditions and received injections of the same solution which was used to suspend the Sedormid. The volume of the injected material and the manner in which it was given were identical for controls and Sedormid-treated eggs.

The effect of giving Sedormid to the chick embryos on different days has not been investigated so far. It is probable that varying the day of embryonic life that the drug is injected will alter the picture in many ways. All of our observations up to the present time have been on this rigidly standardized model which I have described.

In answer to a question about force-feeding of the chickens when they have hatched, I can only say that we have not followed this technique.

Dr. Hsia's comment is very much to the point, namely, that the excretion of unusual amounts of porphyrin or abnormal porphyrins in a variety of diseases as well as in lead poisoning may reflect an intracellular disturbance, the nature of which remains to be elucidated.

Dr. Lowe has asked a highly pertinent biochemical question about the possible relation between the biosynthesis of a pyrrole ring from Δ-aminolevulinic acid and the single carbon fragment which is known to close the purine ring as it enters the C_8. Shemin has recently shown that this relationship does indeed exist. The mechanism by which this probably takes place is that Δ-aminolevulinic acid undergoes oxidative deamination. Thus, the terminal carbon becomes highly active and may then enter the so-called C_1 pool from which it can enter the purine ring (*J. Am. Chem. Soc.* **75**:4873 (Oct. 5) 1953).

PAPERS READ BY TITLE

Digital Blood Flow in the Newborn Infant Measured Calorimetrically. DR. DOROTHY C. Y. YANG, M.MSc. (by invitation), DR. LAWRENCE B. SLOBODY, and DR. MILTON MENDLOWITZ (by invitation), New York.

The amount of blood flowing through the finger or toe can be calculated calorimetrically per unit of surface area per minute. There have been studies reported in adults but not in infants and children. We constructed a small calorimeter to be used for measuring digital blood flow in newborn infants.

The determination is made by measuring the total caloric output of a digit and dividing by the arteriovenous temperature difference. The results are computed according to the following formula:

$$Q = \frac{(\Delta t_1 + \Delta t_2)\ (m + e)}{\rho\ \phi\ a\ (t_a - t_v)}$$

Q is blood flow in cubic centimeters per square centimeter of surface area per minute; t_a, temperature of arterial blood (rectal temperature —0.6 C.); t_v, temperature of venous blood (average calorimeter temperature); ρ, specific gravity of blood; ϕ, specific heat of blood; a, surface area of the finger tip; $\Delta\ t_1$, the rise in temperature of calorimeter in degrees Centigrade per minute with the finger inserted; $\Delta\ t_2$, any fall or rise in temperature per minute in degrees Centigrade not balanced by the heating unit (This change is caused by differences between calorimeter and room temperature, a cork replacing the fingertip); m, the volume or weight of water in the calorimetric cup; e, the hydrothermic equivalent of the cup, thermometer bulb, mercury, and fingertip.

In adults, the average digital blood flow is 0.29 cc. per square centimeter per minute, with a normal range from 0.25 to 0.38 cc. In 20 normal newborn infants from 17 hours to 48 hours of age the average digital flow was found to be 0.09 cc. per square centimeter per minute, with a range from 0.06 to 0.14 cc. (table). Comparison of digital blood flow during the first two days with preliminary results in the later days of the newborn period and in the premature newborn infant will also be presented.

The blood flow per unit of skin surface in the newborn infant is lower than in the adult, probably because of higher viscosity of the blood (higher hematocrit) and lower arterial blood pressure. Whether differences in vascular caliber are an additional factor is unknown.

Studies of the Gastric Mucoprotein Secretion in Infants and Children. Dr. A. Leonard Luhby, Dr. George B. J. Glass, and Dr. Lawrence B. Slobody, New York.

A mucoprotein has been recognized as a major constituent of the gastric juice in man since 1932. Interest in the mucoprotein components of the gastric juice has been stimulated by the recent identification of Castle's intrinsic factor with one of the mucoprotein fractions of the gastric juice. The lack of a simple method for the identification and separation of these mucoprotein components from the other mucinous substances of the gastric juice retarded its study and led to conflicting reports as to its chemical and physiologic nature.

One of us (G. B. J. G.) has developed a simple method to separate and measure the mucinous fractions of the gastric juice. This preliminary study investigates the physiology of the gastric mucoprotein secretion in newborn infants and older children in correlation with the two other major secretory products of the stomach, hydrochloric acid and pepsin.

There are several soluble proteins in the gastric juice which have mucopolysaccharide as a prosthetic group. These mucoproteins must be differentiated from the visible mucus which is not actually in solution. By fractional precipitation with trichloroacetic acid, acetone, and isoelectric adjustment, two groups of mucoprotein-like substances can be separated from normal gastric juice. One of these is a crystallizable material which has a distinct electrophoretic pattern and physiochemical properties which differentiate it from the other soluble mucoids. It is a product of the mucoid cells of the gastric glands and has been termed "glandular mucoprotein." It is with this fraction that intrinsic factor activity appears to be associated.

Studies on glandular mucoprotein secretion in adults reveal that fasting concentrations range from 30 to 150 mg. per 100 cc. Following histamine and vagal stimulation it may reach a concentration of 350 mg. per 100 cc. In conditions associated with atrophy of the gastric mucosa, such as pernicious anemia or atrophic gastritis, mucoprotein concentrations are low or absent. In conditions of excess secretion, as in duodenal ulcer, it is high.

In eight normal newborn infants we found the fasting glandular mucoprotein level to vary from 15 to 26 mg. per 100 cc. In 10 older infants and children ranging in age from 2 months to 8 years, fasting levels varied from 48 to 110 mg. per 100 cc., with the higher levels being found usually after one year of age.

Histamine produces an abrupt but temporary increase of the mucoprotein concentration within the first 15 minutes and then a rapid fall to concentrations as low as one-tenth fasting. Vagal stimulation with intramuscular insulin produces a marked and prolonged increase of the mucoprotein concentration to levels two to three times fasting, which reached their height 60 minutes after insulin. In both of these responses, the secretory pattern of the mucoprotein paralleled that of pepsin rather than that of hydrochloric acid secretion.

The concentrations of hydrochloric acid reached by the newborn infants were at almost adult levels, although the mucoprotein and pepsin concentrations were lower. The latter gradually increased during the first six months toward adult concentrations. Total gastric juice volumes, however, which were one-tenth adult levels in the newborn, did not approach adult volumes until 5 to 6 years of age.

Pattern of Hereditary Susceptibility in Rheumatic Fever. Dr. May G. Wilson, and Morton Schweitzer, Ph.D., New York.

This study is concerned with the pattern of inheritance of susceptibility to rheumatic fever. To investigate the genetic mechanism of inheritance in rheumatic fever the families of a selected parent were brought under observation without regard for the presence or absence of

rheumatic fever in the unselected mate or collateral relatives. The parents selected included 224 members of the Pediatric Cardiac Follow-up Clinic of the New York Hospital, consisting of 192 rheumatic and 32 congenital cardiac patients, 24 consecutive patients with rheumatic heart disease admitted to the Lying-in Hospital, and 43 brothers or sisters of rheumatic members of the Cardiac Clinic. These data are preferable for genetic analysis, since they are not biased by selection of affected children and can therefore be analyzed directly by the application of simple Mendelian ratios. Two hundred ninety-one families, including 646 siblings, were under continuous medical supervision at The New York Hospital for an average period of 10 years. Rheumatic fever occurred in 40 children among a total of 121 offspring in 52 genetically susceptible families. By contrast, in 239 nonsusceptible families with a total of 525 children, there were only 3 children who developed rheumatic fever. Genetic analysis of the data gave good agreement with simple recessive inheritance while excluding other mechanisms. The previous conclusion that susceptibility to rheumatic fever is inherited as a simple recessive trait was corroborated.

Present Status of Passive Prophylaxis in Poliomyelitis. Dr. Lewis L. Coriell (by invitation), Camden, N. J., Dr. Joseph Stokes Jr., Philadelphia, and Dr. W. McD. Hammon (by invitation), Pittsburgh.

A critical analysis is presented of the status of gamma globulin in the prophylaxis of poliomyelitis. Evaluation is indicated at this time because of conflicting reports on the interpretation of the experience in mass and family contact use during the summer of 1953. Review of all available data suggests the following working conclusions:

1. The results of the controlled field trials of 1951 and 1952 still stand and constitute the only statistically reliable data.

There was no evidence in these controlled studies of localization of paralysis due to the injections.

2. Use in household contacts during 1953 was not controlled, and data collected were inadequate to warrant conclusions; therefore it is not profitable to discuss these data, except to point out the inadequacies.

3. Mass use in 1953 when carefully analyzed favors the results of the controlled study in 1951 and 1952. The controls (children not given injections) are unknown, (estimated 10% or less of the population) but a disproportionately large percentage of the paralytic cases occurred in the children not given injections in the areas where gamma globulin was used on a mass scale. Such evidence is suggestive, but not conclusive.

The inadequacies of the controls are presented together with the direction of their bias. Analysis for age distribution and for shift in age groups yields interesting information which will be briefly presented.

Evaluation of the Efficacy of Gamma Globulin in the Prophylaxis of Paralytic Poliomyelitis as Used in the United States During 1953. Dr. Heinz F. Eichenwald (by invitation), Atlanta, Dr. Abraham M. Lilienfeld, M.P.H (by invitation), Baltimore, and Dr. Alexander D. Langmuir, M.P.H. (by invitation), Atlanta.

In 1953, a nationwide effort was made to collect the maximum amount of information concerning the efficacy of gamma globulin when used as a public health measure in the attempted prophylaxis of paralytic poliomyelitis. The study was planned by an advisory committee of 17 authorities on poliomyelitis and was carried out with the full collaboration of the health departments of 41 states and 4 large cities.

Detailed epidemiologic descriptions were obtained from each of the 23 epidemic areas where mass inoculations were given. In five of these communities, measurements of the severity of paralysis were made by specially trained physical therapists on 43 cases developing within one week before the mass inoculations and on 48 cases having onsets following the mass administration.

The most extensive aspect of the program was the study of multiple-case households throughout the country. The severity of paralysis in subsequent cases was studied in relation to whether or not gamma globulin had been received and when given in relation to onset.

The results failed to demonstrate a beneficial effect of gamma globulin.

In 13 of the 23 epidemic areas, gamma globulin was given so late or the population group was so small that no effect could be expected to be demonstrable. In the remaining 10 outbreaks, which occurred in larger communities, gamma globulin was given at or near the peak in only 3 instances. No consistent deviations from the classic patterns of poliomyelitis epidemics were discernible that could be attributed to a beneficial effect of the gamma globulin administration. The severity of paralysis in the selected groups of cases developing immediately before or after mass administration in the five areas showed no differences that suggested a definite modifying effect of gamma globulin.

From the 749 multiple-case households studied, 897 subsequent cases were available for study. Detailed statistical analyses were limited to a refined group of 415 subsequent cases consisting of those white patients 1 to 29 years of age with definite paralytic poliomyelitis occurring subsequent to a definite paralytic index case. Of these 415 cases, 158 received gamma globulin before onset, 184 received no gamma globulin, and 73 received it on or after onset.

The administration of gamma globulin to familial associates of patients with poliomyelitis had no significant influence on (1) the severity of paralysis developing in subsequent cases; (2) the proportion of nonparalytic poliomyelitis occurring in subsequent cases who received gamma globulin before onset; and (3) the classic pattern of familial aggregation of cases in the country at large.

Newer Immunologic Concepts of Smallpox Vaccination. DR. C. HENRY KEMPE (by invitation), San Francisco.

Laboratory and clinical observations made during a recent field study of smallpox conducted in India strongly suggested that many concepts in the field of smallpox vaccination currently held by teachers and practitioners in the field of pediatrics and public health are not in accordance with fact and should be critically reevaluated.

Contrary to general view, smallpox does occur in persons successfully vaccinated. While in nonepidemic regions the duration of protection is considered to be as long as 10 years, in epidemic areas of the world where the challenge is great, successful yearly vaccination is required to protect against smallpox. Over 80% of smallpox patients seen in our study had been successfully vaccinated at least once, but none within the preceeding 12 months.

While it is widely believed that vaccination performed promptly after exposure to a case of smallpox will prevent the disease, the incidence of smallpox under these conditions varies between 10 and 40% in our experience. Vaccination, in order to solidly protect, must be successfully performed before—rather than after—exposure to the disease.

Vaccination is widely thought to be an "all or none" phenomenon; infection either occurs or fails to occur. Our observations indicate, on the other hand, that there is a quantitative as well as a qualitative phase involved and that the degree of antigenic response probably depends on the quantity of virus produced in the skin.

Throughout Asia three or four simultaneous vaccinations are usually produced for primary vaccination, while in some districts two, or only one, insertion is made. All four groups are found in Madras. In 2,000 consecutive cases of smallpox, correcting for the relative ratio of the four vaccination methods in the community, there were 13 times as many cases of smallpox in children having one primary vaccination scar rather than four; five times as many in those having one vaccination scar rather than three; and 2.6 times as much in those having one vaccination scar rather than two. All these scars were the result of simultaneous insertions in primary vaccination and did not represent revaccinations.

There appears also to be definite correlation between the size and severity of single vaccination insertions such as are practiced in this country and the resulting neutralizing antibody level and its duration. This may suggest that our efforts to achieve the smallest possible vaccination take, while increasing public acceptability of the procedure, does diminish antigenic stimulation.

Failure to achieve successful vaccination is usually placed to poor vaccine or faulty technique.

In revaccination, there is evidence that the upper arm may be less susceptible in certain persons—especially if the revaccination site is on or near the areas of previous vaccinations. Such persons can usually be successfully vaccinated on the flexor surface of the forearm. This phenomenon may be one of relative tissue insensitivity due to previous vaccination in the area.

Unsuccessful primary vaccination in infancy and subsequent lack of success with repeated vaccinations in early childhood remain puzzling problems in pediatric practice. Evidence continues to accumulate that passive immunity and the eventual occurrence of subclinical vaccinia are important factors in this phenomenon.

Tetanus Immunization: A Study of Duration of Primary Immunity and the Response to Late Stimulating Doses of Tetanus Toxoid. DR. J. C. PETERSON, Milwaukee, DR. W. C. WILLIAMS, M.P.H. (by invitation), and DR. AMOS CHRISTIE, Nashville, Tenn.

Although the protective value of active immunization with tetanus toxoid has been conclusively established, there remains in the minds of many practitioners and responsible public health personnel doubt concerning the effectiveness of stimulating injections given at relatively late periods after primary immunization. The study was undertaken to determine the duration of

TABLE 1.—*Persisting Immunity*

	Titer					
	< 0.01	< 0.1	< 0.3	< 1.	1. or >	Total
Number	8	42	76	41	46	213

TABLE 2.—*Persisting Levels of Antitoxin According to Immunization Experience*

	Titer					
Experience	< 0.01	< 0.1	< 0.3	< 1.	1. or >	Total
Primary only	3	10	5	4	1	23
Primary + 1 or boosters	3	24	41	29	32	129 *

* Many persons were omitted from this tabulation because there was doubt about their previous experiences.

TABLE 3.—*Response to Booster Immunization*

	Titer					
Days After Stimulation	< 0.01	< 0.1	< 0.3	< 1.	1. or >	Total
6 or 7	0	2	14	5	193	214
13 or 14	0	0	1	0	211	212

protective immunity following basic immunizations with or without stimulating injections and to evaluate the response to booster immunization at dates as long as 10 or 11 years after primary immunization.

Two-hundred nineteen persons were examined in the study. Six are included only in the response studies and five are included only in the persistence studies.

In all, a preliminary blood sample was secured for titration for tetanus antitoxin, and following this, all were given booster immunizations with either one-half or one full dose of alum or fluid tetanus toxoid. The antibody responses following these booster immunizations were examined at 6 or 7 days and at 13 or 14 days.

Nearly all persons had protective levels of antitoxin persisting 1 to 10 years after primary immunization or their last booster immunization (Table 1).

There was distinctly better persistence of primary immunity in those who had received one or more booster or stimulating injections, illustrated in Table 2.

All persons in the study responded well to stimulating injections (Table 3).

The responses of the persons who received fluid toxoid were slightly superior to those of the group receiving adsorbed toxoids.

The capacity to respond to a booster immunization after primary immunization or a preceding stimulus is not materially lessened after 10 years.

However, those with nine or more years elapsing after their last previous stimulus showed a slight delay in response, especially with adsorbed toxoids (Table 4).

Electrophrenic Artificial Respiration in the Newborn. Dr. Heyworth N. Sanford, Chicago, and Dr. Lewis R. Day (by invitation), Denver.

The purpose of this paper is to report on our experiences with electrophrenic artificial respiration as a method of treating apnea neonatorum and congenital atelectasis in the newborn infant. Two stimulating devices were used. The first was made by the Sanborn Company, of Cambridge, Mass., and the second by the Lab-Tronics Inc., of Chicago, known as the L. T. Neuro Stimulator. The babies were treated at the Presbyterian Hospital Premature Station and the Cook County Hospital birth rooms. Atelectasis was generally diagnosed on a clinical basis, though roentgenograms prior to treatment were obtained when possible.

Thirty-seven newborn infants were treated by electrophrenic artificial respiration. Of these, 25 were treated because of apnea in the immediate postnatal period. There were 11 deaths in this group. Of these, three were considered previable. Of the remainder, five were premature infants of 3½ lb. (1,590 gm.) or less. One had severe cerebral hemorrhage, and two showed evidence of severe prenatal asphyxia.

Table 4.—*Response to Booster According to Elapsed Time, Six to Seven Days After Booster**

	Titer					
	< 0.01	< 0.1	< 0.3	< 1.	1. or >	Total
0-3 yr.	..	..	1	..	40	41
9 or > yr.	..	2	..	7	54	63

* Many persons were omitted from this tabulation because there was doubt about their previous experiences.

Twelve infants were treated for atelectasis. There were eight deaths in this group. The four survivals all weighed more than 3½ lb. It was not possible to demonstrate in this series that atelectasis in premature infants was affected by electrophrenic respiration. In full-term infants who survived, roentgenograms were taken a few hours postnatally and showed more air on the treated side.

Electrophrenic respiration seems to excell other methods in certain situations. Because of its lack of versatility, it is not past the stage of experimental development, and we therefore do not recommend it for general use.

Experimental Production of Pulmonary Hyaline Membrane. Dr. Stuart S. Stevenson, and Dr. Leonard E. Lauff (by invitation), Pittsburgh.

The lungs of infants dying with the pulmonary hyaline membrane syndrome show a triad of changes: massive atelectasis, intense capillary engorgement, and a hyaline membrane lining alveolar ducts and alveoli. Experimental work, based upon either the theory of membrane formation from aspirated amniotic fluid or from a pulmonary exudate, so far has failed to reproduce the complete triad.

Weiner, Reid, and Roby (*Science* **110**:190, 1949) demonstrated that fresh amniotic fluid, when it is mixed with plasma, acts like thromboplastin and decreases the clotting time significantly. After confirming this, the authors have attempted to show that both aspiration and exudation are involved in the pathogenesis of the syndrome.

One to two milliliters each of human oxalated plasma and amniotic fluid were introduced by tracheotomy into the lungs of adult guinea pigs. The plasma was from postpartum women and the amniotic fluid was obtained either at the time of elective amniotomy or at Caesarean section. Thirty-nine animals were operated upon under ether anesthesia. This was abandoned because of a high mortality from pneumonia (15 or 38%) and because of the uncertain effects of ether upon the lungs. The subsequent 85 animals received only local anesthesia and were given intramuscular penicillin and streptomycin. Forty of the total of 124 guinea pigs died within 30 minutes, and autopsies revealed acute pulmonary edema with hemorrhage.

The 84 remaining animals died in ¾ to 12 hours (22 of them) or were killed at postoperative periods of 6 to 72 hours. Thirteen showed variations of the triad of pulmonary hyaline membrane disease. Four had thick membranes, and the triad was present throughout the lungs. The remaining nine had definite hyaline membranes accompanied by varying amounts of atelectasis and vascular congestion, but either the membranes were thin or only scattered areas of lung were involved. Limited histochemical procedures have shown that the membranes stain like those found in the human disease. The 13 animals were distributed throughout the series, and no one experimental technique or type of plasma or amniotic fluid gave consistent results.

It is believed that the pulmonary hyaline membrane syndrome has been reproduced in an experimental animal. The work suggests that the human disease may result when aspirated amniotic fluid mixes with an intra-alveolar exudate and expedites its clotting.

Preliminary Report on the Use of a New Microbiologic Assay to Determine the Amino Acid Content of the Blood Plasma in Infants and Children. Dr. Carl C. Fischer (by invitation), Dr. M. John Boyd (by invitation), and Ralph Slonim, B.S. (by invitation), Philadelphia.

As a possible tool to aid in the solution of some of the problems of infants and children with special reference to prematurity, hemolytic disease of the newborn, various nutritional disturbances, etc., a convenient reliable method of determining the amounts of amino acids in the blood plasma would seem to be helpful.

Inasmuch as the majority of the normal figures previously published were based on such relatively nonspecific methods as gastrometric ninhydrin-CO_2 method, nitrous acid method for free amino nitrogen, and semiquantitative paper chromotography, it was felt that the rapid microbiologic assay method with the use of cultures of Clostridiuf perfringens, as originally reported by Dr. M. J. Boyd in the *Journal of Biological Chemistry*, in 1948, might be adapted to this work.

For the past two years studies have been undertaken to apply this method clinically, and as a base line it was decided to determine the normal values of cord blood as compared with maternal blood for methionine, tryptophane, and arginine and histidine.

As a result of these studies, it has been determined that the mean value of the cord plasma methionine was found to be 8.8 γ per milliliter, and the mean value of maternal plasma methionine, 5.9 γ per milliliter, confirming earlier reports that cord amino acid levels are higher than maternal levels but not confirming previous observations that maternal levels are lower than the mean levels for normal adults.

It was also found that the mean value of cord plasma tryptophane was 15.7 γ per milliliter, to compare with the maternal plasma tryptophane of 9.4 γ per milliliter. It will be noted that the mean ratios of plasma tryptophane to plasma methionine of cord and maternal blood are not significantly different, suggesting that similar factors influence the relative concentration of these amino acids in the mother and the fetus and that the placenta plays an active role in amino acid transfer. Figures found in premature infants and abnormal patients are also cited.

Care of the Premature Infant. Dr. R. V. Platou, John H. Rohrer, Ph.D. (by invitation), and Dr. Elaine Allen (by invitation), New Orleans.

This is a very condensed review of a sociologic and psychologic study of the organization and function of nursing services and some aspects of a training program in a large premature infant center. The study was initiated for the purpose of securing pertinent information considered necessary for realistically redefining the duties of graduate nurses and of nonprofessional attendants and for evaluating standards of care as modified by our local circumstances. Current shortages of graduate nurses here and elsewhere have led to the development of care programs which employ progressively more informally trained people working under the guidance of progressively smaller professional staffs.

The Urban Life Research Institute, a basic social science research facility primarily interested in problems arising from social interactions, conducted the study during a full year ending in June, 1953. A variety of study techniques was employed for gathering and evaluating data. During the full year occupied by the study, nearly 1,200 infants weighing less than 2,270 gm.

were admitted for care, and the personnel available were such that on each shift there were from 16 to 36 infants to be cared for by each graduate nurse and from 7 to 17 infants to be cared for by each nonprofessional aide; combining these, from 5 to 11 infants per worker per eight hours.

Conflicts and frustrations, related in large measure directly to years of experience, were found in most cases to be associated with confusion and overlapping of formal assignments as compared with informal assumption of many duties.

The study has served to document and clarify reasons for conflicts among working personnel, thus providing us with intelligent guidance for minimizing frictions which might otherwise defeat our objectives in redefining and formalizing the duties of nurses and attendants. It has again emphasized the importance, as to proper care procedures, of experience gained by informal cribside training as opposed to formal teaching, such as that ordinarily given in regularly scheduled and relatively short courses. It has emphasized a number of inconsistencies and misunderstandings which have interfered seriously with the integration of "care" and "teaching" programs. It has indicated quite clearly the personality characteristics which seem to be required for conspicuous success in caring for premature infants. It has demonstrated that by and large the care of premature infants is very highly routinized. It has furnished a well-documented set of yardsticks which we hope to apply intelligently in our next move—that of realistically reexamining our standards and procedures according to our local resources and problems.

Finally, it is certainly not the intention of this study to set up a new set of standards for anyone else or to find particular fault with previously published recommendations we found so valuable in planning our own program. We do emphasize, however, that any guides available for this or any similar project, involving numerous social interactions, must require modifications based on periodic studies of this type.

Evaluation of Current Standards for Hospital Care of Premature Infants. Dr. Paul Harper, Rowland V. Rider, Sc.D. (by invitation), Dr. Hilda Knobloch (by invitation), Dr. Patricia Husson (by invitation), and Sara Fetter, B.S., R.N., Baltimore.

This paper reports the first part of a long term-study of prematures undertaken cooperatively by the Johns Hopkins University School of Medicine Division of Maternal and Child Health and the hospitals, physicians, and health and education agencies of Maryland. Data including positive confirmation of survival have been obtained on more than 98% of the 4,700 prematures born in Maryland in 1952. Each of the 46 hospitals that admitted these babies was visited at the start and at the end of the study year to determine its facilities and staff arrangements for care of prematures during the year; hospitals were then divided into groups on the basis of conformity to recognized standards (American Academy of Pediatrics Committee on Fetus and Newborn: Standards and Recommendations for Hospital Care of Newborn Infants, 1948, was the primary source of standards). Larger hospitals show greater conformity with these standards than do smaller hospitals.

The group of hospitals were compared as to the neonatal survival rate of prematures. Preliminary tabulations suggest that there is no important difference between the various hospital groups in survival of prematures with a birth weight above 2,000 gm.

Correlations are made between survival and such factors as race, parity, socioeconomic status, amount of prepartal care, complications of pregnancy, labor, and delivery, differences in obstetrical practice, and postnatal course of the baby in the hospital. The influence of these findings on performance of the various hospital groups is discussed.

Similar data will be presented on all babies born at home during both 1952 and 1953.

Additional information is given concerning various hospital practices, such as age at which feeding is begun, duration of incubator care, and length of hospital stay by birth weight groups and by hospital groups.

Growth and Development of Negro Infants: V. Neuromuscular Patterns of Behavior During the First Year of Life. Dr. Roland B. Scott, Dr. Angella Ferguson, and Dr. Melvin E. Jenkins, Washington, D. C.

This investigation was undertaken to determine the time of occurrence of certain neuromuscular patterns of behavior in the development of Negro infants during the first year of life. In designing this study, an attempt was made to parallel a similar investigation by Aldrich,

who followed the development of 215 white infants through 12 behavioral steps, namely, smiling, vocalization, head control, hand control, rolling, sitting, crawling, prehension, pulling up, walking with support, standing alone, and walking alone.

Approximately 250 or more infants were studied in each of the above categories; one-half of the infants were from two well-baby clinics where no fee was charged, and the remainder were from private pediatric practice. Only healthy full-term infants were included in the study. The subjects were seen at monthly intervals in order to determine as accurately as possible the occurrence of behavior patterns.

When all of the infants in this study were compared with the white infants in the Rochester Project, the neuromuscular development of the Negro infants was consistently accelerated with the exception of one pattern, smiling.

In a comparison of all three groups (white private infants in the Aldrich study, the Negro private infants, and the Negro clinic infants) the free-clinic infants showed accelerated motor development over the other groups for the first 35 weeks of life. After the 35th week, the development of the two Negro groups was essentially the same.

The private white and Negro infants showed a marked similarity in development during the first 30 weeks of life, after which time there was a trend toward acceleration in the Negro private group.

The differences observed in neuromuscular behavior in these study groups may be attributed in part to environmental factors.

Study of the Concentrations of Protein (and Partitions), Urea, Glucose, Hydrogen Ions, CO_2, Chlorides, Sodium, Potassium, in the Sera of Premature Infants Weighing 1,500 Gm. or Less on the First Day of Life. Dr. Joseph B. Pincus (by invitation), Dr. Isaac F. Gittleman (by invitation), Dr. Masayuki Saito (by invitation), and Albert E. Sobel, Ph.D. (by invitation), Brooklyn.

Premature infants weighing 1,500 gm. or less were studied on the first day of life before any feedings of parenteral fluids were administered. Blood samples were obtained by heel puncture as soon after the baby's birth as possible. Each individual serum was examined for pH, CO_2, sodium, chloride, potassium, urea, glucose, total protein, albumin and globulins (alpha 1, alpha 2, beta, and fibrinogen and gamma).

We found that the pH range was from 7.1 to 7.42, the CO_2 from 24 to 53.5 vol. %. The total protein concentrations varied from 4 to 5.6 gm. per 100 cc. The albumins varied from 47.5 to 65% of the total. The gamma globulins, with one exception, varied from 9.9 to 12.5% of the total. The glucose concentration range was from 28 to 130 mg. per 100 cc., and the urea from 8 to 42 mg. per 100 cc. The serum chlorides concentration varied from 93 to 110 mEq., the sodium from 127 to 142 mEq., the potassium from 6 to 9 mEq.

Our results would indicate that premature infants weighing 1,500 gm. or less on the first day of life and who were perfectly normal on physical examination, except for their prematurity, tended to have a pH on the acid side of "normal" though in several instances the pH had normal values. The CO_2 concentrations, on the other hand, were surprisingly "high," lying well within the range of values considered normal for the premature infant. The chlorides were within the normal range of values. The sodium concentrations were relatively low. The potassium values were high. With one exception they were above the highest values given for the normal range of potassium in the sera of mature infants. Total protein concentrations were low. The gamma globulin concentrations were half the normal values given for full-term normal infants.

Evaluation by Oximetry and Cord Blood Determinations of Babies Born by Caesarian Section. Dr. Loren G. MacKinney (by invitation), and Dr. Frances Ehrlich (by invitation), Buffalo.

The neonatal death rates in the maternity wing of the Buffalo Children's Hospital in 1952 following Caesarian section and low forceps delivery were 3.1 and 0.56%, respectively. To better understand the causes for the higher section death rate, a comparative study was made of 134 babies delivered by Caesarian with a group of 341 delivered by low forceps. Evidence was sought of oxygen deprivation of the section babies at birth and their failure to achieve normal arterial O_2 saturation as compared with the low forceps group. Twenty-five determina-

tions of maternal arterial O_2 saturation were obtained during delivery for comparison with that of their newborn offspring.

Cord blood was used to determine the arterial O_2 saturation.

Babies born by Caesarian section have lower O_2 content and saturation in cord blood than babies born by low forceps. This greater relative anoxia may explain the difference in mortality.

Feeding of Premature Infants. Dr. B. M. Kagan, Dr. J. H. Hess, and Evelyn Lundeen, R.N. (by invitation), Chicago.

The purpose of this study was to compare the weight gains of groups of premature infants fed four different feedings.

One of the feedings was human milk. The second was cow's milk modified so that the protein, carbohydrate, and fat concentrations were similar to those of human milk. The third was human milk modified by increasing the protein and decreasing the fat concentrations. The fourth was a half-skimmed cow's milk mixture providing high protein and low fat concentrations.

One hundred fifty-six infants were studied. Isocaloric feedings were used.

The mean birth weight was 1,482 gm. Among the larger infants there were significant differences in mean weight gain between each of the differently fed groups. In order of largest to smallest gains, the feedings were half-skimmed cow's milk mixture, cow's milk modified to simulate human milk, modified human milk, and human milk. In those of smaller birth weight, the relationships were the same except that the difference between the mean weight gain in the two groups gaining the most was not significant.

At the regular intervals the milks were analyzed chemically. There was no relationship between weight gain and the protein or fat concentrations of the various milks. However, when the total ash intake per day per kilogram of body weight was plotted against the weight gain in grams per kilogram of body weight, the mean figures for the four groups made a remarkably straight line.

The differences in weight gain between the various groups are not due primarily to the differences in calories supplied by protein or fat. The most important single factor appears to be the ash. Since the ability of premature infants to excrete electrolyte is relatively poor, the differences in weight gain between the groups would seem to be due principally to relative retention of electrolyte and water.

The details and significance of the findings will be discussed.

Cytomegalic Inclusion Disease in Infancy. Dr. James B. Arey (by invitation), Philadelphia.

The morphologic alterations in the viscera and in the central nervous system of an infant dying at the age of 12 months are described. A diagnosis of generalized cytomegalic inclusion disease had been established shortly after birth by the demonstration of the characteristic inclusion bodies in the urine and in fluid obtained by "subdural" puncture. The infant's immediate neonatal course was characterized by hepatomegaly, splenomegaly, thrombocytopenia, purpura, and icterus. Although for a time the configuration of the head was that of a microcephalic, subsequently enlargement of the head occurred with the appearance of hydrocephalus.

At postmortem examination, performed at the age of one year, the most striking macroscopic finding was the presence of hydranencephaly. The cerebral hemispheres were replaced by a thin-walled uniocular cystic structure filled with fluid; for the most part the walls of the sac were paper-thin, but in a few areas islands of cerebral cortex could be identified. The thalami were recognizable at the base of this cystic structure; the aqueduct of Sylvius was occluded. The histologic findings in the central nervous system will be described.

Histologic examination of the viscera revealed small numbers of the characteristic inclusion bodies of cytomegalic inclusion disease; these were located in the submaxillary gland, thyroid, duodenum, and kidney. In the submaxillary gland there were multiple foci of lymphocytic infiltrate, some of which were closely associated with the inclusion-bearing cells. Similar focal aggregates of lymphocytes were present in the kidney, but these were not associated with demonstrable inclusion bodies.

The findings suggest that disappearance of the cells of cytomegalic inclusion disease may occur over a period of time, leaving only residual chronic inflammatory foci upon which a specific diagnosis cannot be established. The significance of these findings and the possible relation of hydranencephaly in this infant to cytomegalic inclusion disease are discussed.

Newly Observed Syndrome Simulating Pituitary Dwarfism. Dr. Richard Wagner, Boston.

A syndrome characterized by markedly retarded growth in height, retarded osseous differentiation, sexual infantilism, and a congenital anomaly of the heart has been observed in 12 children. The anomaly of the heart is not considered the primary cause of the retarded development.

The syndrome is sex-linked. All patients included in this study are males. The triad of retarded growth and development, a congenital anomaly of the heart, and retarded osseous differentiation constitutes the inherent pattern of the syndrome. If the carriers of the syndrome reach the age of puberty, they reveal sexual infantilism. As in other syndromes with multiple congenital anomalies in childhood, other stigmata, particularly mesenchymatous in origin, occur frequently but not regularly. In this particular syndrome one of the other stigmata is a peculiar skeletal anomaly, "pseudoepiphyses," on one or more of the metacarpal bones. The site of predilection is the proximal end of the second metacarpal bone. Less frequently they are found on the proximal end of the fifth metacarpal and the distal end of the first metacarpal. They were present in 8 of these 12 patients.

A relation between pseudoepiphyses and endocrinopathies has been suggested by several investigators. Rochlin, for instance, thought that when they were present, sexual infantilism was to be expected at the age of puberty. From our observations we do not consider it correct to classify them as accessory independent epiphyses and hence a normal variant, but that they have the same significance as the skeletal stigmata in other congenital syndromes, such as the deformity of the middle phalanx in Mongolism, a radioulnar synostosis, and deformities at the sternal ends of the ribs.

All of our patients were below the expected height of their age group. The retardation amounted to from 3 in. (7.6 cm.) in the younger children to 13 in. (33 cm.) in the older boys. The osseous differentiation lagged by one to four years behind the chronological age, according to Todd's standards.

An exact diagnosis of the anomaly of the heart can not be established so far. In all cases there was a systolic murmur along the left border of the sternum, best heard in the third intercostal space. In some of the cases the murmur had a harsh rasping quality. There was no thrill.

Two of our patients who reached the age of puberty revealed complete sexual infantilism. There was no evidence of pituitary dwarfism or primary hypogonadism in either of these patients. Further observation of the younger children when entering the age of puberty, sex hormone studies, and testicular biopsies will be contributory to the final classification.

Further Observations on Blood Corticoids in the Newborn Infant. Dr. R. Klein (by invitation), Dr. C. Papadatos (by invitation), J. Fortunato, M.S. (by invitation), and C. Byers, B.S. (by invitation), Pittsburgh.

It was reported last year that newborn infants have circulating free corticoids which are much lower than the average for older infants and children. These observations have been extended in number and confirmed. The mean level of 17,21-dihydroxy-20-ketosteroids in the infants from 2 to 5 days of age is 1.5 γ per 100 ml. of serum. Bongiovanni suggested that conjugated corticoids be measured, since the significance of this low level of circulating corticoids could not otherwise be assessed. Using a modification of the Nelson-Samuels technique for measuring blood corticoids wherein acid hydrolysis of the serum was carried out, it was found that the level of the conjugated corticoids of the newborn infant does not account for the low level of the free circulating corticoids. The average level of conjugated serum corticoid in 16 newborn infants was 14 γ per 100 ml. of serum.

In addition, the response of the adrenal to stress, as measured by the serum corticoid levels, will be presented. Up to the present moment no newborn child has been seen who did not respond to stress with a rise in circulating corticoid. The stresses studied have been infection, operation, and the administration of corticotropin (ACTH).

Clinical and Experimental Observations on Alopecia Areata and Totalis. Dr. Reginald Wilson, F.R.C.P.(C) (by invitation), Dr. Stuart Maddin (by invitation), and Dr. Julius Danto (by invitation), Vancouver, B. C., Canada.

The pathogenesis of this disease is still one of the major enigmas of medicine. Although many hormones have previously been used with doubtful therapeutic success, there is growing evidence that endocrine factors do play some part in its genesis. In support of this the following attributes of the disease have been emphasized, i. e., the severity in cases of prepubertal onset, the amelioration which occurs during pregnancy and lactation, and the frequent relationship to the onset of thyrotoxicosis.

It is known that rheumatoid arthritis shares some of these clinical characteristics. For this reason and the knowledge that rheumatoid arthritis responds to cortisone, one of us used cortical steroids in the treatment of alopecia. It was found that these substances will stimulate regrowth of hair in alopecias of this type. This has been confirmed by others. The consistency of this initial response in cases of long-standing disease, the direct relationship to dosage, and the fact that the phenomenon can be repeated at will, preclude the possibility that this is a fortuitous response in a condition which is notorious for spontaneous remissions.

These results and the presently reported observations in 10 more cases (4 children, 6 adults) indicate the probability that the progress of early cases of areata can be reversed with cortisone or corticotropin (ACTH). Severe cases (totalis) of short duration respond while under treatment but may relapse when treatment is stopped. In some instances where prolonged maintenance therapy is used, a permanent result may be obtained in totalis but in severe cases of long duration temporary regrowth is to be expected only while treatment is sustained. The final results in totalis cases are not sufficiently certain to be clinically practical.

In spite of the therapeutic limitation of cortisone treatment, the fact that the germinal epithelium can be stimulated even temporarily may prove of great experimental value. The need for further study of this phenomenon was obvious. In particular, more information was required regarding the histochemical tissue changes which occur during this drug-induced remission. Precise information is also lacking in regard to estimations of circulating cortisone in these patients.

In considering further investigation of this problem, the authors were reminded that alopecia totalis shares some clinical characteristics with other diseases which have alterations in the collagen matrix and respond similarly to cortisone. This leads us to consider the possibility of changes in the collagen fibers in alopecia.

In an attempt to provide more information on these points, the electron microscopic appearance of the collagen was examined in two patients with long-standing disease. They were reexamined after administration of cortisone. These biopsy findings have been compared with control sites and in healthy untreated volunteers.

The clinical observations include data regarding dosage, duration of treatment, late clinical results, photographs, and side-effects. Experimental results include observation of hematoxylin and eosin biopsies and electronmicroscopy of collagen.

Demand Feeding Reconsidered. Dr. Charles Hendee Smith, New Brunswick, N. J.

Before the birth of pediatrics—75 years ago—babies were fed, from the breast or bottle, whenever they cried, no matter how often. One of the first accomplishments of pediatricians was to train mothers to use regular feeding schedules. At first the interval was every two or three hours for all. Then 50 years ago the four-hour interval became the rule, except for small babies or prematures. This plan worked well when used with common sense. A few mothers did become overanxious, feeding their infants with too meticulous exactness, exceptions which did not invalidate the soundness of the principle of regular feeding.

Of late new prophets have arisen in the land, preaching that a baby must be fed "on demand," lest he be "frustrated." Demand feeding has been widely accepted. Young pediatricians regularly order it, and lay magazines contain many articles extolling its virtues as the only correct method. The experience of three-quarters of a century is thrown overboard.

What is the result?

To any man with an active practice are brought a large number of babies who have reacted badly to demand feeding. The theory behind it presupposes that every infant will regulate himself, will take no more than he needs, without danger of overfeeding. The formulas prescribed order more than the baby needs so that he may take all he wants when he wants it. No regard is paid to the known food requirements of the infant, which many pediatricians seem to have forgotten. The mother is supposed to know when the baby is hungry, but she is given by nature a terror lest her offspring starve, and to her all crying means hunger. She can not differentiate the dozen other causes of crying. Therefore the baby is fed too much and too often, and inveitable effects of overfeeding ensue, i. e., anorexia, often following an inordinate weight gain, digestive upsets with vomiting and diarrhea, or an intractable eczema. Babies with symptoms due to overfeeding promptly improve when regular feeding of proper amount is prescribed.

The mother also profits from a regular schedule, for she has a life of her own to lead, a family and a home to manage. On demand feeding she can make no plans, keep no engagements or appointments, for she never knows when the baby will have to be fed. Without exception, the distracted mother eagerly welcomes a planned day, so that she can regulate her life, her work, and her scant leisure. She is often pathetically grateful.

The regular schedule need not be too rigid. The night and early morning feedings should be given when the baby wakens, but the day feedings should be given approximately on time, even if he must be wakened or has to wait a little, i. e., the baby regulates the night, the mother the day feedings.

The conclusion is that experience shows that demand feeding often leads to symptoms which are relieved by regular feeding. The mother needs a planned schedule as much as does the infant.

Absorption of Hemagglutinins. Dr. J. M. Bowman (by invitation), Winnipeg, Man., Canada.

In view of the still-existing uncertainty as to whether breast feeding is harmful to infants with hemolytic disease of the newborn, 15 infants were fed on the first day of life with human sera containing high titer natural and immune hemagglutinins. Hemagglutinin titers before and at intervals after feeding the sera were measured and will be presented.

Effect of Surface Active Agents and Trypsin on Sputum. Dr. Edward Wasserman (by invitation), and Dr. Lawrence B. Slobody, New York.

Surface active agents and enzymes are being used therapeutically as an aerosol for respiratory diseases. There has been a lack of laboratory evidence to support the claims of clinical efficacy.

Two properties of these agents were selected for testing at this time: (1) ability to reduce viscosity; (2) ability to reduce surface tension. The method for determining viscosity is a modified apparatus based on that used by Basch, Holinger, and Poncher. The bubble method was used for determining surface tension.

The following were selected for comparative studies on sputum: sodium lauryl sulfate (Dupinol C); methylbenzethonium chloride; Triton A-20, sodium bicarbonate, glycerin (Alevaire); sodium octyl sulfate (Tergitol O8); and trypsin (Enzar). Normal saline solution was used as a control.

Sputum was collected and homogenized. The surface tension and viscosity of the sputum were determined before and after the addition of the individual agents in various dilutions. Trypsin is far superior to the four other agents tested in reducing viscosity.

The surface active agents are effective in reducing surface tension and are superior to trypsin in this respect.

A limited number of clinical studies will be presented, comparing the surface tension and viscosity of sputa from the same person before and after treatment with these agents as an aerosol.

Studies on the Proteinuria and Hematuria of the Nephrotic Syndrome. Dr. Walter Heymann, Cleveland.

The effect of corticotropin (ACTH) and cortisone on the proteinuria of 15 nephrotic children was studied. Daily quantitative determinations of urinary proteins were carried out during 22 courses of either corticotropin or cortisone. Three children in four courses failed to diurese, and no decrease of proteinuria was noted. Eighteen treatments resulted in diuresis, and a decrease of proteinuria was observed in these children, without exception, two to nine days prior to the onset of the diuresis. It was also found that the degree of the initial hypoproteinemia is related to the time elapsed between first noted decrease of proteinuria and diuresis onset. These results suggest that the diminishing proteinuria is an important factor in the mechanism of the hormone-induced diuresis.

The dependence of proteinuria on protein intake has been studied in five nephrotic children. High- and low-protein diets appreciably affected the urinary protein losses in four children within 24 hours. The same dependence of proteinuria from protein intake has been studied in the experimental disease of the rat. It was found that the hyperlipemia decreases during low- and increases again during high-protein periods and that the incidence of uremia increases greatly when the animals are kept on high-protein diets.

The nephrotic hematuria frequently produces a bright red urine, while the gross hematuria of acute glomerulonephritis usually gives rise to a more brownish tinge. The nephrotic hematuria seems to be correlated to a certain extent with the intensity of proteinuria. This was suggested from observations made (1) on 4 corticotropin- and cortisone-treated nephrotic children with hematuria; (2) on 14 nephrotic children who were treated with intravenous injections of concentrated salt-free human albumin. Six episodes of transient hematuria were noted, while proteinuria increased during albumin administration.

The albumin-globulin ratio and the total amounts of albumin and globulin excreted in the urine of 30 nephrotic children were determined by electrophoresis with the Tiselius method. Over 60 determinations were carried out at various intervals over a one-and-one-half-year period. A high globulin excretion in excess of 2 gm. per 24 hours seems to indicate a progressive malignant course of the disease.

Further Experience with Corticotropin (ACTH) and Cortisone Maintenance Therapy in the Treatment of the Nephrotic Syndrome. Dr. Kurt Lange, Dr. Ruth Strang, Dr. Lawrence Slobody, and Eugene J. Wenk, M.S., New York.

The nephrotic syndrome should, in all probability, be considered the result of an extensive antigen-antibody reaction, since serum complement is characteristically lowered in this disease. In our recent studies, it could be shown that the excretion of complement or one of its components into the urine cannot account for the fall in serum complement. The amounts of complement components excreted into the urine are relatively small; this occurs in any disease with severe proteinuria and does not necessarily lead to a lowering of serum complement levels (Kimmelstiel-Wilson disease, severe amyloidosis of the kidney). Individual components of complement excreted vary widely from case to case.

The pattern of lowering of components of complement in the serum of patients with the nephrotic syndrome closely simulates the pattern of complement component removal found when isolated rat kidneys were perfused with nephrotoxic sera known to be capable of producing the nephrotic syndrome in rats. It is also similar to the pattern seen in vitro in typical immune precipitates.

In the nephrotic syndrome, corticotropin (ACTH) or cortisone, by depressing antibody formation, will effect a rise in serum complement. After short courses of corticotropin or cortisone thearpy, serum complement often falls again to subnormal levels because of full resumption of antibody formation. With the aim of depressing antibody formation over a long period of time, maintenance therapy with corticotropin or cortisone was carried out during the last 36 months.

Twenty-one patients with the nephrotic syndrome were observed carefully on maintenance therapy for 6 to 36 months (average, 22 months). Six cases received corticotropin (100 mg.

for three successive days of each week), 15 patients were given 400 mg. of oral cortisone on three successive days of the week for 6 to 52 weeks. This followed an initial course of corticotropin (100 to 160 mg. per day for seven days), which had led to diuresis.

During maintenance therapy, proteinuria disappeared in the four cases treated within three months of the onset of the disease. In all other cases the degree of proteinuria was markedly reduced and blood chemistries returned in all cases rapidly to normal.

During this therapy, our observations have been as follows. Maintenance therapy is valuable only when the initial course of corticotropin successfully induces complete diuresis with rise of complement to normal. Maintenance therapy has to be started within a few days after the initial course of therapy. Small doses of cortisone are ineffective for maintenance therapy because, with small doses, relapses may develop. When high doses of cortisone were given, no relapses occurred during maintenance therapy. Maintenance therapy must be continued for long periods of time to prevent recurrences of the disease, secondary to upper respiratory infections or sensitization reactions producing a recall phenomenon. An increase in proteinuria is the earliest sign of recurrence of disease and precedes the fall in serum complement. Serum complement falls a few days prior to the development of edema. After prolonged maintenance therapy, patients may develop moderately increased proteinuria subsequent to an upper respiratory infection, but they frequently do not progress to edema formation. The increased proteinuria may disappear within a short time without retreatment.

In the group on maintenance therapy there have been no major untoward effects, even in small children. There has been no apparent impairment of the rate of growth and development, and there have been no fatalities. All patients are at present free of edema and have no proteinuria or varying low amounts of proteinuria.

Neonatal Tetany in Two Siblings: Effect of Maternal Hyperparathyroidism. Dr. R. Lee Walton (by invitation), Syracuse, N. Y.

Two white female siblings were born approximately one year apart, birth weights, 2,045 and 1,678 gm., respectively. Both infants developed neonatal hypocalcemic tetany, which was slowly responsive to antitetanic therapy.

Because of the occurrence of persistent neonatal hypocalcemic tetany in these two prematurely born siblings, the 27-year-old mother of the siblings was subjected to medical investigation. She was found to have hypercalcemia, hypophosphatemia, and nephrocalcinosis. Surgical exploration of her neck revealed a parathyroid adenoma, which was removed.

One should suspect, therefore, primary hyperparathyroidism in mothers of infants with neonatal tetany, and especially in prematurely born, Negro, and breast-fed infants, since the occurrence of tetany in these infants is unusual.

Secondary maternal hyperparathyroidism occurring during pregnancy has also been implicated as an etiologic factor in producing neonatal hypocalcemic tetany. A theory is presented to show that the transplacental effects of primary and secondary maternal hyperparathyroidism are mediated by parathormone and not by Ca or P ions.

An apparently increased number of stillbirths, prematurely born infants, and miscarriages in the mother described here is pointed out.

The values for serum ionized calcium, calculated by use of the McLean-Hastings Nomogram, in the mother and her two offspring are discussed.

Graduate Teaching of Pediatricians in a Children's Outpatient Department. Dr. Barbara Korsch (by invitation), and Dr. Samuel Z. Levine, New York.

In recognition of the need for increased emphasis on outpatient department work in pediatric training, on the graduate as well as undergraduate level, the New York Hospital-Cornell Medical Center has been providing a systematic fellowship training program in the Pediatric Outpatient Department. This training program has been in operation since 1942, but has existed in its present fully developed form only for the past five years.

The submitted paper will contain a description of the content of this training program: (1) the program of rotation through general and special pediatric clinics (including metabolism, renal, cardiac, allergy, neurology, hematology, pulmonary, adolescent, and premature follow-up Clinics), (2) the opportunities for long-term follow-up of well babies and children as well

as of children with acute and chronic illness, (3) the training in normal child development offered in the New York Hospital Nursery School, (4) the series of teaching conferences for inpatient and outpatient department staff (clinical pathological conference, pediatric x-ray conference, follow-up conference, interdepartmental conferences, seminars on growth and development and emotional problems in childhood, case discussions, therapy conferences, and special lectures). The specific teaching and supervision offered to the pediatricians in training during their fellowship will also be described.

It will be pointed out that a number of basic requirements must be met in order to maintain a high-standard of teaching and service in a children's outpatient department: (1) an adequate number and variety of patients, (2) an appointment system that insures adequate time for each patient visit and continuity of patient-doctor relationship, (3) a separate room for each clinic physician, (4) continuous close supervision of the pediatricians in training by senior staff members, (5) opportunity to provide supervised experience in the subspecialties of pediatrics as can be done in the special pediatric clinics, (6) opportunity to provide training in health supervision, preventive medicine, and guidance of parents as can be done in the well-baby clinics, general pediatric clinics, and adolescent clinics, (7) adequate ancillary services of all types required to maintain as high a standard in the diagnosis and treatment of ambulatory pediatric patients as usually prevails in the care of the hospitalized patients, (8) close integration with a pediatric inpatient service, (9) availability of consultants from pertinent specialties, e. g., psychiatry, surgery, orthopedics, dermatology, gynecology, neurology, eye, ear, nose and throat, and urology, so that pediatricians in training can get a broad viewpoint of pediatric care and learn techniques and timing of referrals.

Thirty-five pediatricians have served as fellows in the outpatient department, 22 of them in the last five years. Most of the fellowships were for one year, a few only for six months. Questionnaires were recently sent to the group of former fellows, and the replies will be summarized in the submitted paper, with special emphasis on areas where the fellowship training was reported to fill in gaps left after traditional hospital training and in areas where concrete suggestions for improvement and future planning were presented.

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

COMPOSITION OF THE ADULT HUMAN BODY AS DETERMINED BY CHEMICAL ANALYSIS. R. M. FORBES, A. R. COOPER, and H. H. MITCHELL, J. Biol. Chem. **203**:359, 1953.

Analytical data on a man aged 46 are given for the body as a whole and for a number of separate tissues. Weights of various organs are given in terms of per cent of total body weight. Values for water, fat, protein, calcium, and phosphorus content are presented. For the body as a whole, water content was 55.1% of body weight; fat, 19.4%; protein, 18.6%; calcium, 1.9%, and phosphorus, 0.9%. Comparison of these values with those obtained by other workers for fetuses and newborn infants is of interest.

FORBES, Rochester, N. Y.

INFLUENCE OF DIETARY AUREOMYCIN AND CARBOHYDRATE ON GROWTH, INTESTINAL MICROFLORA, AND VITAMIN B_{12} SYNTHESIS OF THE RAT. G. E. PETERSON, E. C. DICK, and K. R. JOHANSSON, J. Nutrition **51**:171 (Oct. 10) 1953.

G. E. Peterson and co-workers fed weanling rats a purified diet deficient in vitamin B_{12}, and noted that growth was faster with dextrin as the sole dietary carbohydrate than when sucrose was used. When chlortetracycline (Aureomycin) was incorporated (100 ppm) in these rations, growth was stimulated, even when the rations were fortified with vitamin B_{12} (25 γ per kilogram of body weight). The intestinal microflora were rapidly changed with the feeding of chlortetracycline. The concentration of "free" vitamin B_{12} was significantly greater in the intestines of the rats reared on chlortetracycline-containing diets; a high correlation was noted between the growth response and the intestinal concentration of "free" B_{12}. The inability of chlortetracycline to influence tissue storage of vitamin B_{12} substantiates the results of others. By fortification of the diet with B_{12}, the concentration of B_{12} in the kidney and liver was increased.

FREDEEN, Kansas City, Mo.

RIBOFLAVIN METABOLISM OF WOMEN ON CONTROLLED DIETS. MEI-LING WU, EVELYN WARREN, and CLARA A. STORVICK, J. Nutrition **51**:231 (Oct. 10) 1953.

The authors studied riboflavin metabolism in seven adult women on a controlled diet. The diet met the recommended allowances of the National Research Council in all known nutrients, except for thiamine and riboflavin. There appeared to be no relationship between the the concentration of riboflavin in the serum and the riboflavin intake. The effects of an oral test dose of riboflavin were studied. The concentration of riboflavin in the serum reached a peak in one-half to one hour after the test dose and approached the fasting level in five hours. The peak in urinary excretion of riboflavin occurred one hour after the test dose, and by the fifth hour the excretion of riboflavin was about the same as the one-hour fasting excretion.

FREDEEN, Kansas City, Mo.

THE EFFECT OF MUCIN ON THE GROWTH OF RATS FED SIMULATED HUMAN MILK. R. M. TOMARELLI, E. LINDEN, G. T. DURBIN, and F. W. BERNHART, J. Nutrition **51**:251 (Oct. 10) 1953.

Tomarelli and co-workers found that the addition of mucin, as a potent source of a microbiological growth factor also present in human milk, to diets formulated to approximate the composition of human milk stimulated the growth of weanling rats. The destruction of the microbiological growth activity of mucin by prolonged acid hydrolysis also resulted in a loss of the rat-growth activity.

FREDEEN, Kansas City, Mo.

THE INFLUENCE OF DIETARY FAT AND CARBOHYDRATE ON GROWTH AND LONGEVITY IN RATS. C. E. FRENCH, R. H. INGRAM, J. A. URAM, C. P. BARRON, and R. W. SWIFT, J. Nutrition **51**:329 (Nov. 10) 1953.

Male and female rats receiving a high fat diet (22.7% fat) grew fully as rapidly as those on a carbohydrate diet (3.4% fat), according to the authors, although they consumed 4.8 and 5.7% less total calories, respectively. The life span of the male rats ingesting the high fat diet decreased markedly, and there was also a less pronounced but significant decrease in the longevity of the females. Increased efficiency of utilization of the diet was correlated with decrease in life span, but increased caloric intake per se was not so associated. The livers of males on the high fat diet contained significantly more fat than those of males fed the carbohydrate diet. The present data indicate that a high fat diet decreased the life span without noticeably altering the cause of death. The commonest disease recorded was chronic pneumonia with bronchiectasis, which was found in about 90% of the male and 70% of the female rats on all diets. Hematuria and general infections were more prevalent in the males, while mammary gland tumors were found more frequently in the females.

FREDEEN, Kansas City, Mo.

INFLUENCE OF GLUCOSE ON AMINO ACID METABOLISM. H. N. MUNRO and W. S. T. THOMSON, Metabolism **2**:354 (July) 1953.

The effects of ingestion of dextrose (50 gm.) and butter (30 gm.) on the concentrations of amino acids in the plasma were measured in six fasting men. Two hours after ingestion of dextrose, isoleucine, leucine, valine, arginine, threonine, tryptophan, and histidine were all found to be reduced in concentration by amounts varying from 36% (isoleucine) to 8% (histidine). The effects of fat ingestion were much less marked and of doubtful statistical importance. Contrary to previously published reports, there was no evidence to substantiate the view that dextrose ingestion causes an immediate fall in tryptophan excretion in the urine.

KAPLAN, New York.

IODINATED PROTEIN IN MILK. L. VAN MIDDLESWORTH, A. H. TUTTLE, and ANN THRELKELD, Science **118**:749 (Dec. 18) 1953.

A portion of the radioactivity appeared in all the various protein fractions of dog milk when the lactating animal was fed radioactive iodine. Purified casein also contains some protein-bound iodine.

FORBES, Rochester, N. Y.

IDIOPATHIC HYPOPROTEINAEMIC OEDEMA AND AMINO-ACIDURIA IN AN INFANT. J. P. BOUND and W. R. HACKETT, Arch. Dis. Childhood **28**:104 (April) 1953.

The case of an infant who had hypoproteinemic edema from birth is described. The serum albumin concentration was persistently low, and γ-globulin was virtually absent. The presence of intermittent amino-aciduria is emphasized. There was a history of a sibling with hypoproteinemic edema, for which no cause was found. It is postulated that both infants suffered from an inherent abnormality of amino acid metabolism manifested chiefly as idiopathic hypoproteinemia. In both widespread staphylococcal infections developed. Tocopherol had very little, if any, effect on the progress in the present case.

KELLY, Milwaukee.

TESTS AS TO THE EXCRETION OF CHLORAMPHENICOL THROUGH THE MOTHER'S MILK. L. MARTONI and V. MAGLIETTA-POLLARI, Clin. pediat. **35**:830 (Nov.) 1953.

Twelve nursing mothers were given 0.5 to 1.0 gm. of chloramphenicol by mouth; milk was expressed from their breasts four hours later and tested for the presence of the drug. No active chloramphenicol was found in any of the samples by biological tests. Chemical tests were not done, as with chemical tests, inactivated derivatives of the drug (nitrocompounds) would have given positive tests.

HIGGINS, Boston.

THE EFFECTS OF BILE AND OF CHOLINE ON THE INTESTINAL ABSORPTION OF FATS BY INFANTS. L. LANDUCCI and M. L. CHITI, Clin. pediat. **35**:835 (Nov.) 1953.

Fat-balance tests were made on 18 infants 1 to 2 months of age, and the percentage of fat unabsorbed by the intestines was determined. Each of the infants had "dyspeptic" stools; only 59 to 87% of the fat fed was absorbed. Following these preliminary tests, each child was given either 4 drops of a 10% solution of dried bile four or five times a day for one week, or 0.125 gm. of choline four times a day for a similar period. Fat-balance tests then were repeated, and the fat absorption was found to have increased 5 to 25%. Tests with each medication on the same child seemed to indicate that the choline hydrochloride was the more efficacious in increasing fat absorption.

HIGGINS, Boston.

Hygiene; Growth and Nutrition; Public Health

THE SOCIAL AND ECONOMIC IMPACT ON MEDICINE OF THE CONTROL OF INFECTIOUS DISEASES. PERRIN H. LONG, Illinois M. J. **104**:349 (Dec.) 1953.

In this paper, Long discusses the social and economic impact on medicine of the control of infectious diseases. He points out that a score or more of organizations are receiving and disbursing annually many millions of dollars of the public's money for specific health purposes. Charitable foundations have made, and will continue to make, large financial contributions for the support of various phases of medical education and research. Federal, state, and municipal governments are contributing billions of dollars to the support of medical care and research. The health sciences have become "big business." As the author states, it is time to analyze what has been accomplished, what may be accomplished, and what problems currently have been created, or may arise, as a result of advancing knowledge in the health sciences. A one-sided effort in this field, not coordinated with current or developing social, economic, and political forces, could produce dire results.

If one looks back 100 years, one finds that the annual mortality rate was nearly double what it is now. In any understanding of what has happened in relation to health, careful attention must be given to the general awakening of the human mind which followed the Renaissance. Political, social, philosophical, and scientific thinking were newly oriented, and while they did not proceed, and are not proceeding, apace, extensive developments in all areas of thought have had their influence on the health of our people.

One must give the major credit, as far as the remarkable progress which has been made in promoting longevity and increasing and maintaining certain aspects of health is concerned, to the scientists, clinicians, and public health workers in the field of infectious diseases and processes. The major improvements in health which have been recorded in the last 100 years are the results of the control of infections by serotherapeutic or chemotherapeutic and antibiotic agents. Decreases in the mortality rates are primarily due to the control of infectious diseases by public health methods, improved environmental conditions, and the wane of certain pandemic diseases.

Health scientists should take stock of their efforts during the past 50 years and attempt to evaluate the results. Consideration should be given to the effects of the saving of lives on longevity or expectation of life and the composition of our population, as such relates to its distribution by age groups. More than 20 years of life expectancy have been added in the lifetimes of most of us. It appears that in the United States we have almost reached the maximum of increase in life expectancy that can be gained by the control of infectious processes. In 1951, but about 20% of the deaths occurring in persons under 15 years of age in this country were due to infections.

The net result of the savings in life that have been made in the last 75 years, and which have increased at an accelerated rate during the past 25 years, has been to bring about a considerable change in the age distribution of the population in the United States. Today it is estimated that in a total population of 159,000,000 people, the aged (65 years and over) number more than 14,000,000, and that possibly within another 25 years this figure will reach 24,000,000. These changes in our population should cause everyone, especially physicians, to stop and think. We have, in more than one sense, created this situation, and our triumph will be an empty one unless the difficulties of the older folks are faced and reasonable solutions found.

BARBOUR, Peoria, Ill.

Prematurity and Congenital Deformities

MANDIBULOFACIAL DYSOSTOSIS. P. HUWITZ, A. M. A. Arch. Ophth. **51**:69 (Jan.) 1954.

Mandibulofacial dysostosis is a rare congenital malformation of the facial bones, first described in 1889, by Berry. At that time it also became known as the "Treacher Collins syndrome." There are five forms of the disease: (1) complete; (2) incomplete, in which the deformity is less marked, the ears may be almost normal, but deafness is usually present; (3) abortive, in which only the lid anomalies exist; (4) unilateral, with hypoplasia of the muscles of the face and other symptoms on one side, and (5) atypical.

The palpebral fissures are involved; the malar bones and the mandibles show hypoplasia; malformation of the external ear, and occasionally of the middle and inner ear, is found; high palate and irregular disposition of the teeth, fistulae between the angles of the mouth and the ears, atypical hair growths, facial clefts, and other anatomical deformities occur. Additional features include mental retardation, harelip, clubfoot, and synostosis of the joints. The less salient features are ocular, nasal, oral, aural, and other bony defects of the skull.

The hereditary aspects of the condition have been proved by its appearance in several generations. It seems to have an irregular, dominant form of transmission. The treatment, naturally, depends upon the possibilities of plastic surgery, individual for each case and determined by the deformity.

SPAETH, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

BLINDNESS OF PREMATURE INFANTS. ARLINGTON C. KRAUSE, Illinois M. J. **104**:370 (Dec.) 1953.

Blindness in infants from infection and trauma has been reduced to a low level, but congenital blindness is increasing rapidly. The commonest cause is retrolental fibroplasia, which appears in the early months of life and frequently leads to blindness. The etiology may be related to the postnatal metabolism. There is no specific treatment,

BARBOUR, Peoria, Ill.

CASE OF CONGENITAL HEMIHYPERTROPHY SHOWING VARIATIONS IN BONE AGE AND DEVELOPMENT. J. STEPHEN CARTER and G. C. DOCKERAY, Arch. Dis. Childhood **28**:321 (Aug.) 1953.

A case of left-sided congenital hemihypertrophy with necropsy findings is reported.

Roentgenologically, the carpal bones showed apparent advancement of bone age on the affected side, but retardation in development of the epiphyses of the metacarpals and phalanges on the same side, combined with an abnormal structure of the bones themselves.

As certain internal paired organs within the embryonic segments affected by the hypertrophy were found to be equal in size at necropsy, namely, testes and adrenal glands, it is considered unwise to assume a diagnosis of congenital total hemihypertrophy on external appearances alone.

KELLY, Milwaukee.

IONOGRAM OF THE PLASMA OF THE PREMATURE INFANT. I. SALA and I. FRIED, Lattante **24**:134 (March) 1953.

An ionogram presents the picture of the electrolyte balance, in this study, of the blood plasma of 12 premature infants, 12 to 66 days old and weighing 1,700 to 2,500 gm. As compared with normal infants, the premature infants showed in their plasma more potassium, sodium, chlorides, phosphates, sulfates, and organic acids, as well as a lower alkali reserve (CO_2-combining power); there was also a small diminution in the amount of plasma protein.

HIGGINS, Boston.

MANDIBULOFACIAL DYSOSTOSIS. S. LO BIANCO, Lattante **24**:860 (Nov.) 1953.

The cases of three children with mandibulofacial dysostosis are reported. In this condition there is micrognathia and failure of the maxilla to develop properly. Two of the children had microcephaly and were retarded mentally. There was also a tendency to dwarfism. One of the children had bilateral cataract.

HIGGINS, Boston.

Newborn

HEARING TEST FOR NEWBORN INFANTS. JULIUS B. RICHMOND, HERBERT J. GROSSMAN, and SEYMOUR L. LUSTMAN, Pediatrics **11**:634 (June) 1953.

A simple, readily reproducible test of gross hearing in the newborn infant is presented. Although the test is particularly applicable to adoption problems, it is suggested that this examination be adopted as standard procedure in all nurseries as a part of the routine evaluation of the neonate.

FROM THE AUTHORS' SUMMARY.

ROENTGEN FINDINGS IN SKULL AND CHEST IN 1,030 NEWBORN INFANTS. ANDREW P. DEDICK and JOHN CAFFEY, Radiology **61**:13 (July) 1953.

Specific x-ray findings discussed in this article are mineralization of the nasal bones, herniation of the pulmonary apices, fracture of the clavicle, ossification centers for the interparietal bone, accessory occipital ossicles, hyoid body, hyoid horns, anterior arch of the atlas, coracoid processes, and humeral heads.

In a larger group, 5,000 infants, hypoplasia with poor mineralization of the nasal bones occurred in 0.15%. Fifty per cent of these hypoplastic infants were found to have mongolism. In five children with mongolism observed in an older group who had lived more than 10 years the nasal bones were not mineralized.

Ten infants in the authors' group showed air-containing lung above the first rib, and, although a diagnosis of an apical hernia was made, the condition was not considered significant in the first days of life.

Several charts are presented showing the incidence of ossification centers and herniation of the lung apex in different groups, with consideration given to the mothers' age and the infants' weight.

ANSPACH, Chicago.

SCLEREMA ADIPOSUM NEONATORUM. M. B. ABAD, Philippine J. Pediat. **2**:49 (Jan.-March) 1953.

Sclerema neonatorum is reviewed. Its causes of confusion are pointed out. Two cases of patients who have recovered are presented, and an outline of probably adequate treatment is suggested.

FROM THE AUTHOR'S SUMMARY.

ON THE COMPARATIVE USE OF SILVER NITRATE AND PENICILLIN IN THE EYES OF THE NEWBORN. HOWARD MALLEK, PETER SPOHN, and JOSEPHINE MALLEK, Canad. M. A. J. **68**: 117 (Feb.) 1953.

Studies were conducted over a 16-month period using penicillin ointment and silver nitrate in alternate months in the eyes of the newborn. Irritation occurred infrequently in the penicillin groups and was attibutable to frequent handling to instill repeated doses of a weak ointment. When a strong concentration was used, 100,000 units per cubic centimeter, no irritation occurred. Irritation was present in almost every case in which silver nitrate was used. No infections occurred in either group. The authors feel that penicillin is a safe substitute for silver nitrate. A single application of ointment containing 100,000 units per cubic centimeter is sufficient.

HYPERPYREXIA IN POST-KERNIKTERUS SYNDROME. W. H. PATTERSON and R. M. FORRESTER, Arch. Dis. Childhood **28**:217 (June) 1953.

A syndrome in infants is described in which the main features are neck retraction, profuse sweating, and hyperpyrexia of central origin.

Of nine cases described, eight were fatal. In eight there had been severe neonatal jaundice, and in six of these definite evidence of nervous involvement ("clinical kernicterus") in the neonatal period had been shown.

Seven of the infants had suffered from hemolytic disease of the newborn.

One of the infants suffered from familial acholuric jaundice.

The possible mechanism of the disturbance is discussed.

KELLY, Milwaukee.

SIGNIFICANCE OF HYALINE MEMBRANES IN THE NEWBORN. MARCEL LELONG, RENE LAUMONIER, and LETAN VINH, Études néo-natal. **2**:3 (March) 1953.

The present study is based on 31 cases; postmortem examination was always performed within the first 24 hours, and in 17 cases, within the first 10 hours.

Anatomical Features of the Hyaline Membranes.—They are never encountered in the cylindric epithelial parts of the bronchi; they are predominant in the bronchioles, the primitive aerial pathways of the premature, and the alveoli of the full-term infant, which are precisely the site of the largest vascular connections. Usual stainings show a definite acidophile tendency; in our observations the membranes appear in red-brown with the Van Gieson technique. Some observations are made in connection with the previous features; amniotic aspiration is shown by the presence of the cornified cells, but their number is variable—in half of our cases, no cornified cells were found, in 11 cases they were rare, in only 4 cases were they often encountered. No meconial aspiration was observed.

Pulmonary lesions are associated with hyaline membranes; leucocytic inflammation of the pneumonic type, vasomotor reactions, degeneration and necrosis in the middle of the membrane or in the center of the alveolus, with pyknotic nuclei originating from the proximal epithelial cells.

The authors would like to emphasize the discrepancy between the continuous disposition of the membranes and the discontinuity of the channelled epithelium of the premature.

Chemical Nature of the Hyaline Membranes.—Fats: The fatty substances do not originate from vernix but are the result of cell degeneration.

Proteins: If their staining features and aspect give them the appearance of protidic-like substances, it is impossible, however, to characterize them; fibrin colorations are negative.

Glucides: Hotchkiss test is always positive, which evidences the presence of a mucopolysaccharide (in agreement with Miller's observations). Membranes of a similar constitution might be observed after rheumatic fever with carditis, grip, streptococcal pneumonia, intoxication by gases (phosgene), interstitial plasmocytic pneumonia, milk embolism. They are completely similar to the neonatal ones.

In a search for reproducing the membranes experimentally, we have observed typical membranes after bilateral vagotomy in the rabbit.

Conclusions.—The authors' observations seem to rule out an amniotic origin or a degenerative one (from the alveolar walls).

The hyaline membranes of the newborn resemble the other ones observed in older infants or in asphyxic animals with inflammatory lesions. If we could have a better knowledge of the chemical structure of exudates into the alveolar cavity, it might be the clue to our problem.

FROM THE AUTHORS' SUMMARY.

ADMINISTRATION TO THE MOTHER DURING LABOR OF DL-α-TOCOPHEROL: THE EFFECT OF RETENTION OF TOCOPHEROL IN THE CORD BLOOD. A. MINKOWSKI, J. NEUMANN, and N. CAILLEBOTTE, Études néo-natal. **2**:33 (March) 1953.

In view of the fact that tocopherol level in the plasma of the premature is low (14) and that the administration of a supplementary intake of 300 to 600 mg. of dl-α-tocopherol acetate to the mother raises the vascular resistance of the premature newborn (8 to 10), we have compared the tocopherol level in the cord blood of 28 subjects after supplementary intake to 28 in the control series with the following observations:

1. After a supplementary intake (300 to 1,500 mg.), the average tocopherol level is increased as compared with the control series, with a statistically valid margin (526 against 390).

2. After a supplementary intake, the tocopherol level in the cord blood is never low, whereas it occurred seven times in the control series.

3. It is not necessary to give more than 300 mg. of tocopherol to obtain such results.

FROM THE AUTHORS' SUMMARY.

OBSERVATIONS AND CALCULATIONS CONCERNING METABOLISM IN NEWBORN INFANTS. C.-E. RÄIHÄ, Études néo-natal **2**:93 (June) 1953.

According to the calculations of fetal capacity to take up glucose from maternal circulation, it is made plausible that a considerable part of fetal need of oxygen is covered by oxygen liberated from sugar when sugar is converted into fat. This fact ought to be consistent with a metabolism which is characterized by an ample presence of pyruvic acid and co-carboxylase and a scarce presence of cytochrome c in fetal tissue.

FROM THE AUTHOR'S SUMMARY.

AGRANULOCYTOSIS IN THE NEWBORN PERIOD. LISELOTTE SCHÜMER, Arch. Kinderh. **147**:164, 1953.

The author presents a discussion of the literature, etiology, and manifestations of agranulocytosis. It is obvious that the prognosis during childhood seems to be better than in adults. A report is given of a 7-day-old infant with purulent periumbilical inflammation, leucopenia (with a count of 1,800), and normal bleeding and coagulation times. Penicillin, streptomycin, oxytetracycline (Terramycin), and transfusions did not produce signs of immediate effect. The author was under the impression that there was a gradual spontaneous recovery. The most probable etiologic factor is an allergic reaction, as has been described by Lehndorff.

GOTTSTEIN, Chicago.

INCOMPATIBILITY OF BLOOD GROUPS AS CAUSE OF ICTERUS NEONATORUM. H. HOFFBAUER and H. J. PETTENKOFER, Deutsche med. Wchnschr. **78**:214 (Feb. 13) 1953.

The ABO blood grouping and the Rh factor of mother and child were investigated in 483 births in relation to icterus neonatorum. The appearance of "physiological" icterus neonatorum was not dependent on ABO incompatibility or on Rh factors.

AMBERG, Rochester, Minn.

EARLY VOMITING OF THE NEWBORN AND CARDIOESOPHAGEAL RELAXATION. P. DEMOULIN and P. BONHOMME, Acta pædiat. belg. **7**:38, 1953.

The case of a girl who began to vomit on the second day of life is described. Roentgenograms showed reflux of the contrast medium in a dilated esophagus. Treatment consisted of placing the child in an upright posture for prolonged periods. Roentgenograms taken three months later showed normal findings. The authors advise early treatment of these patients because of the danger of peptic esophagitis, which may even become hemorrhagic.

GLASER, Jerusalem.

ERYTHROBLASTOSIS FETALIS IN THE BLOOD GROUP "KELL." J. J. VAN LOGHEM JR., D. DE RAAD, and A. VAN HATTEM, Maandschr. kindergeneeesk. **21**:63 (Feb.) 1953.

A case of hemolytic disease of the newborn due to isoimmunization by the blood group "Kell" is described. The child suffered from a severe form of icterus gravis, with multiple skin hemorrhages which disappeared rapidly after two exchange transfusions. The clinical course was uneventful.

Nine other cases of immunization by the "Kell" factor have been described in the literature or revealed by personal communication. The frequency of the blood group "Kell" in the Netherlands is 8.5% (investigation of 538 random blood samples). The genotype frequencies are KK, 0.19%; Kk, 8.30%; kk, 91.51%.

During recent years eight sera were found in our laboratory containing antibodies anti-"Kell," in six cases combined with anti-Rh antibodies. The anti-"Kell" serum described in the present article, and a second one, which caused a blood transfusion reaction, did not contain additional immune antibodies.

In five of these cases, the antibody was the result of blood transfusion; three times anti-"Kell" was formed during pregnancy.

FROM THE AUTHORS' SUMMARY.

HEMOLYTIC DISEASE OF THE NEWBORN IN THE FIRST-BORN BABY. S. I. DE VRIES, M. A. VAN BOUWDIJK BASTIAANSE, and J. I. DE BRUIJNE, Nederl. tijdschr. geneesk. **97**:1385 (May 30) 1953.

The authors report a case in which an Rh-negative mother received intramuscular injections of Rh-positive blood during pregnancy. The child born to her recovered from the resulting hemolytic disease after exchange transfusion. The intention of the report is to direct attention to the fact that not only in giving blood intravenously it is necessary to examine the blood groups of patient and donor, but also in giving blood intramuscularly. VAN CREVELD, Amsterdam.

Acute Contagious Diseases

RELATIONSHIP OF TONSILLECTOMY TO POLIOMYELITIS. T. C. GALLOWAY, J. A. M. A. **151**:1180 (April 4) 1953.

Reports from various centers have led to conclusions that are difficult to evaluate. Experimental and clinical data have not clarified the real relationship of tonsillectomy to poliomyelitis.

Galloway has diligently searched for statistics and has given much thought to the evaluation thereof.

From his study of the evidence, he concludes: "Tonsillectomy does significantly increase the incidence of bulbar poliomyelitis when done during epidemics. The over-all incidence is probably increased but perhaps only by the increase of bulbar poliomyelitis. Elective tonsillectomies should be restricted in epidemic periods. Investigation should be made of a similar relationship of dental and other oral and general operations to poliomyelitis and the need of restricting them in epidemic."

GORDON, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

BETAINE AND GLYCOCYAMINE IN TREATMENT OF POLIOMYELITIS. ARTHUR L. WATKINS, New England J. Med. **248**:621 (April 9) 1953.

Nine cooperative adults who had had paralytic poliomyelitis over one year prior to the present study were given betaine and glycocyamine, and the effect of these compounds on weakened muscles was evaluated. One patient with paralysis of the legs as a sequela of infectious polyneuritis was also studied.

Standardized techniques for measuring muscle strength were used.

The medication produced no intolerable side-effects, but no subjective sensations of improvement were experienced. Only 26% of the muscles tested showed as much as a 20% increase in strength, and hence there was no subjective or functional significance in the statistical improvement.

Betaine and glycocyamine were considered to have no appreciable value in the treatment of the residual muscle weakness resulting from poliomyelitis in the patients under consideration.

WHEELOCK, Denver.

BETA-PYRIDYLCARBINOL (RONIACOL) POLIOMYELITIS. H. L. H. DICK, PAUL PARKER, and BRUCE TILL, Northwest Med. **52**:544 (July) 1953.

The authors report on the clinical effectiveness of β-pyridil carbinol (Roniacol) in the relief of the muscle pain of poliomyelitis. They conclude that β-pyridil carbinol is at least as effective as tolazoline (Priscoline) and, since it appears to be much safer, deserves further clinical trial.

DOCTER, Seattle.

EXPERIMENTAL POLIOMYELITIS: STUDIES IN MICE WITH HUMAN GAMMA GLOBULIN. S. J. KLEIN and J. M. ADAMS, Proc. Soc. Exper. Biol. & Med. **83**:308 (June) 1953.

A 10% suspension of virus-infected brains and spinal cords was titrated by intracerebral inoculation of white mice to determine the $L.D._{50}$ in 0.03 ml. Gamma globulin from pooled human plasma was mixed in various amounts with the virus. It was found that the dose of gamma globulin necessary to protect mice against poliomyelitis intracerebrally was several thousand times the amount which was effective by in vitro neutralization. The prophylactic effect of

gamma globulin was maximal with a dose of 4 ml. per kilogram of body weight injected peritoneally when given four days before the inoculation of the virus intracerebrally. At 7 to 14 days the protection had apparently disappeared.

HANSEN, Galveston, Texas.

ACTIVE BASAL IMMUNITY AND ITS APPLICATIONS TO EPIDEMIOLOGY: I. GENERAL CONSIDERATIONS. HANS ERICSOON, LENNART HESSELVIK, and B. VAHLQUIST, Acta pædiat. **42**:540 (Nov.) 1953.

Some general immunological considerations and their practical application in immunization prophylaxis are discussed as an introduction to subsequent papers.

FROM THE AUTHOR'S SUMMARY.

ACUTE DIFFUSE GLOMERULONEPHRITIS AFTER FIRST VACCINATION. L. KOSTER and J. Q. VAN TILBURG, Nederl. tijdschr. geneesk. **97**:17 (Jan. 3) 1953.

Three cases of acute glomerulonephritis after a first vaccination against smallpox are described. All three patients were boys of the age of 18 to 20 years. The main symptom was hematuria. In two cases a chronic nephritis developed.

VAN CREVELD, Amsterdam.

Acute Infectious Diseases

SALMONELLOSIS COMPLICATED BY PANCARDITIS. G. R. HENNIGAR, R. THABET, W. E. BUNDY, and L. E. SUTTON JR., J. Pediat. **43**:524 (Nov.) 1953.

The authors present a case of pancarditis due to Salmonella Group C-1 in a 2-year-old Negro boy with severe diarrhea. Autopsy findings are presented.

MACDONALD, Pittsburgh.

INFECTION DUE TO PYOCYANEUS BACILLUS IN INFANTS. ROBERT CLEMENT and L. MILLARD, Presse méd. **61**:661 (May 9) 1953.

Pathogenic activity of Bacillus pyocyaneus, which has been experimentally demonstrated, is also proved by the existence of septicemia, meningitis, cutaneous and visceral manifestations, development of agglutinins, and characteristic necrotic and hemorrhagic changes.

General infections, recognizable by the presence of the Bacillus in the blood or by a suppurative focus, assume especially the appearance of a severe septicopyemia, with cutaneous changes of eschar type and various visceral involvements. Meningitis, more often secondary than primary, is one of the gravest locations of the infection.

The role of Pseudomonas aeruginosa in certain severe diarrheas of infant seems unquestionable, and also in certain severe cutaneous manifestations, superinfection of burns, wounds, or eczema, otitis, laryngitis, and pulmonary lesions.

Treatment is particularly difficult, owing to the resistance of B. pyocyaneus to most antibiotics; with the use of antibiograms it is now possible to select the most effective association of antibiotics. Polymyxin B so far appears to be the medicament of choice in infections due to B. pyocyaneus.

FROM THE AUTHORS' SUMMARY.

CHRONIC MYOCARDITIS DUE TO CHAGAS' DISEASE IN CHILDREN. R. R. DE SOUZE, E. SILVA, F. GAVOTTO, A. MARTIRANI, and A. MANISSADJIAN, J. pediat. (Rio de Janeiro) **18**:344 (March-April) 1953.

Eight cases of Chagas' disease in children are reported and discussed. Special emphasis is placed on the cardiac complications which were evident in three of these children.

FROM THE AUTHORS' SUMMARY.

TIN IN TAPEWORM THERAPY. RICHARD KUHLS, Med. Klin. **48**:1511 (Oct. 9) 1953.

Cestodin tablets contained metallic tin, tin oxide, with a small addition of tin chloride. The amounts are not given here. The tablets have been used successfully in tapeworm infestation with Taenia solium and saginata, as well as with Bothriocephalus. The activity seems to be directed against the head and adjoining part, so that these parts are destroyed by action of the

digestive juices. Since the head cannot be detected in the dejecta, the effect of the cure has to be determined by follow-up examination. Among the 202 patients aged 9 to 82 years, 12 were children below the age of 15 years. In none of these was recurrence noted. Altogether, recurrences were noted in 16 patients, and, of these, 4 responded to repeated therapy.

AMBERG, Rochester, Minn.

CLINICAL OBSERVATIONS DURING AN EPIDEMIC OF PARATYPHOID. J. HERMANNSEN, Med. klin. **48**:1543 (Oct. 16) 1953.

In an institute for recuperating children, a sudden outbreak of a paratyphoid epidemic occurred. Of 500 children, 298 became ill with various clinical manifesations of the paratyphoid infection. In 7% the disease was severe; that is, the patients had fever for three or more weeks. No noteworthy complications were seen, and no fatality occurred, even without chloramphenicol (Chloromycetin) treatment.

AMBERG, Rochester, Minn.

HEMOPHILUS INFLUENZAE PRODUCING ACUTE AND CHRONIC INFLAMMATORY PROCESSES. KRUNA TOMIĆ-KAROVIĆ, Wien. klin. Wchnschr. **65**:940 (Nov. 13) 1953.

From a swelling on the anterior neck of a 7-year-old patient pus was obtained. From this pus the bacillus Hemophilus influenzae was isolated, as well as Sarcina aurantiaca. In other cases of prevalent infections, such as vulvovaginitis and urethrism in adults, the Hemophilus bacillus could be isolated.

AMBERG, Rochester, Minn.

AN EPIDEMIC OF INFECTIOUS LYMPHOCYTOSIS. J. DOCHAIN and A. LAMBRECHTS, Acta pædiat. belg. **7**:230, 1953.

The authors found 10 cases of infectious lymphocytosis in a girls' orphanage. Alerted by the first three girls, who had fever and a considerable degree of lymphocytosis, the authors came upon other cases of lymphocytosis (21,000 to 63,000 leucocytes; 75 to 95% lymphocytes) in routine examinations of clinically well children. Mild gastrointestinal, respiratory, or menigeal symptoms may occur in some of the patients.

The literature is reviewed.

GLASER, Jerusalem.

RHEUMATIC PNEUMONIA. D. P. R. KEIZER, Nederl. tijdschr. geneesk. **97**:741 (March 21) 1953.

The case history of a 10-year-old boy who fell acutely ill with signs of pneumonia and hemorrhagic sputum is reported. Treatment with sulfadiazine was followed by deterioration. Penicillin also had no effect. After eight days symptoms appeared of rheumatic fever with carditis, which subsided quickly after treatment with sodium salicylate; the pneumonia also improved. A diagnosis of rheumatic lung infection was made.

VAN CREVELD, Amsterdam.

TULAREMIA AT HORN. G. D. HEMMES, Nederl. tijdschr. geneesk. **97**:990 (April 18) 1953.

Tularemia is reported for the first time in the Netherlands. In one family six cases occurred after the eating of a hare, which had been found dead. Symptoms consisted of acute chills, aching head and limbs, high fever, diarrhea, and small ulcers in the mouth. In two patients the lungs were also affected. All patients recovered. Agglutination tests and a guinea pig test with material obtained from the remnants of the hare confirmed the diagnosis. No other case could be demonstrated in the neighborhood, either in man or in animals.

VAN CREVELD, Amsterdam.

PARINAUD'S CONJUNCTIVITIS AND CAT-SCRATCH DISEASE. A. W. C. VAN VEELEN and P. D. STIBBE, Nederl. tijdschr. geneesk. **97**:1203 (May 9) 1953.

A girl seen in 1948 suffered from Parinaud's conjunctivitis. She had an intermittent fever for 10 days and swelling with suppuration of the preauricular lymph nodes on the side of the conjunctivitis. The pus from the lymph nodes was bacteriologically sterile. In 1952 an intracutaneous test with Mollaret's antigen was positive. The conjunctivitis was therefore probably caused by the virus of cat-scratch disease.

VAN CREVELD, Amsterdam.

BENIGN LYMPHORETICULOSIS AS CAT-SCRATCH DISEASE. H. B. G. BREIJER and R. GISPEN, Nederl. tijdschr. geneesk. **97**:1849 (July 11) 1953.

A patient was seen with swelling of the lymph nodes of the axilla two months after being scratched by a cat. The diagnosis of cat-scratch disease was made and confirmed by a positive cutireaction with Mollaret's antigen. After repeated evacuation of pus from the suppurated nodes, the symptoms disappeared in two weeks.

Sera of 5 patients with cat-scratch disease with a positive cutireaction and a negative Wassermann reaction were examined for antibodies with a lymphogranuloma venereum antigen; 3 of these sera showed a significant fixation of complement, whereas a similar reaction was shown by only 5 out of 78 arbitrarly chosen sera with negative Wassermann reactions.

VAN CREVELD, Amsterdam.

CAT-SCRATCH FEVER. D. P. R. KEIZER, Nederl. tijdschr. geneesk. **97**:1958 (July 25) 1953.

Three children were seen with cat-scratch disease. The diagnosis was confirmed by a positive cutireaction with Mollaret's antigen. One patient had swelling with suppuration of the lymph nodes of the axilla. The symptoms disappeared two weeks after incision and drainage of the node. In the other two children there had been contact with cats. One patient had generalized lymph node swelling with fever for a week after he received a wound on his knee and suppuration of a node in the neck six weeks after injury. One patient had swelling of the lymph nodes in the axillae, appearing two weeks after she received a small wound on the hand and subsiding without suppuration within three weeks.

VAN CREVELD, Amsterdam.

COMBINED TREATMENT OF INFECTIOUS DISEASES WITH REFERENCE TO BACTERIAL RESISTANCE. A. Manten, Nederl. tijdschr. geneesk. **97**:2720 (Oct. 17) 1953.

The advantages of combined therapy over treatment with a single drug are summarized. Special emphasis is placed on the fact that combined treatment suppresses bacterial resistance. This effect is explained on the basis of the genetics of the bacteria. The practical value of combined treatment is demonstrated by examples taken from the literature.

VAN CREVELD, Amsterdam.

Chronic Infectious Diseases

FIVE-YEAR FOLLOW-UP OF 100 CASES OF MILIARY AND MENINGEAL TUBERCULOSIS TREATED WITH STREPTOMYCIN. KENNETH M. SMITH, Am. J. M. Sc. **225**:657 (June) 1953.

The 2½- and 5-year survival figures for 100 cases of acute disseminated miliary tuberculosis and tuberculous meningitis treated with combined intramuscular and intrathecal injections of streptomycin are presented.

The patients were in Veterans Administration Hospitals and consisted of four groups, with varying mortality. After five years, 47% of those with only miliary tuberculosis at the time therapy was begun are alive, while none who developed tuberculous meningitis subsequent to therapy for miliary spread are alive. Twelve per cent of patients with only tuberculous meningitis are alive, and only 4% of those with combined miliary and meningeal tuberculosis remain living. All deaths due to tuberculosis occurred in the first two and a half years following therapy.

SUTTON, Evanston, Ill.

EPIDEMIOLOGY OF TUBERCULOSIS. GAYLORD W. ANDERSON, Am. Rev. Tuberc. **67**:123 (Feb.) 1953.

The past 50 years have shown a striking decline in tuberculosis mortality and morbidity; the 1951 figure for mortality in the United States is one-tenth that which was found in 1900. Several factors are to be consdered: the shift of peak mortality from the younger into the older age groups, the decline in infection rates, the increase in BCG vaccination, and improved methods of treatment. All factors are involved in the decline; no one factor is solely responsible in a given area or country. The rate in certain other countries, especially the Scandinavian, has declined more rapidly than in the United States and Canada.

These studies of tuberculosis mortality further emphasize the importance of the family, especially its adult members, as the crucial epidemiological unit in the development of tuberculosis. These adults are the victims, as well as the sources, of infection. Control programs should be directed at this concept.

ROYCE, Pasadena, Calif.

TREND OF TUBERCULOSIS MORTALITY. JULIUS KATZ, Am. Rev. Tuberc. **67**:279 (March) 1953.

Studies of tuberculosis mortality which are based only on the number of deaths and reported cases show that there has been no decrease in the number of new cases of tuberculosis discovered each year. This has been interpreted as a failure of the preventive phase of the tuberculosis campaign. If the number of persons examined—a number which increases each year—is considered, a truer incidence is found. Figures taken from such studies in upstate New York show a diminishing yield in the percentage of new cases of tuberculosis.

ROYCE, Pasadena, Calif.

CHEMOTHERAPY OF MILIARY TUBERCULOSIS AND TUBERCULOUS MENINGITIS. PUBLIC HEALTH SERVICE COOPERATIVE INVESTIGATION, Pediatrics **12**:38 (July) 1953.

Ninety-three children with tuberculous meningitis, 23 of whom also had miliary tuberculosis, were observed for a period of one year while under treatment with a combination of tuberculostatic agents. One-half of the patients were given streptomycin intramuscularly, streptomycin intrathecally, and paraaminosalicylic acid and thiazolsulfone (Promizole) by mouth. The remainder were on an identical regimen except that thiazolsulfone was omitted.

Forty-two patients (45%) survived the first year; 24 of these had no sequelae of the disease. No differences were noted in the course of the disease between those who received thiazolsulfone and those who did not, and the one-year survival rates in the two groups were practically identical.

Revision of the streptomycin dosage, which took place after the study had been in progress seven months, produced results which appear to justify the change. An intramuscular streptomycin dose of 50 mg. per kilogram b.i.d., to a maximum of 1.5 gm. twice daily, was apparently more effective than 20 mg. per kilogram b.i.d.

Edith M. Lincoln, whose results in childhood meningitis are the most successful of those yet reported, and the British Medical Research Council both depend on a regimen which includes intrathecal administration of streptomycin. The investigators in this study favor its use and had no unusual difficulty with it.

Relapse occurred in eight children, all of whom survived the first year.

A poorer prognosis was noted in infants, in nonwhite children, and in patients with miliary tuberculosis.

The commonest toxic effects were due to streptomycin, which caused vestibular damage in a large number of patients, but the capacity of children to compensate for this dysfunction is so great that the risk is minor in the face of the otherwise hopeless outcome. Streptomycin may have been partially responsible for marked hearing losses in six instances.

Paraaminosalicylic acid and thiazolsulfone act less rapidly than streptomycin. They are easily administered and rarely produce significant toxicity, even when given over extended periods. They appear to reinforce the effect of streptomycin, and paraaminosalicylic acid, at least, postpones the emergence of streptomycin resistance. Their use appears to decrease the likelihood of relapse. Finally, their daily use at home maintains the patient's awareness that he requires prolonged medical supervision and brings him back for examination when his drug supply needs replenishing. The use of these drugs with streptomycin in tuberculous meningitis is therefore recommended.

FROM THE AUTHORS' SUMMARY.

PRIMARY TUBERCULOSIS IN THE CHILD: PRESENT CONCEPTS OF THE PROBLEM; THERAPY. R. PIERRET, A. BRETON, and J. RATEL, Pédiatrie **8**:23, 1953.

The anatomopathological, experimental, and clinical pictures of primary tuberculosis and the problems of diagnosis and particularly of treatment are discussed.

The failure of antibiotics to improve cases of primary tuberculosis, especially of the lymph node type, and the protective action of the antibiotics against the hematogenous spread in the secondary phase of the disease place before the physician an important and difficult decision as to whether to use an expensive and dangerous treatment in a child who might not need it or to risk fatal hematogenous spread. Various other factors in border cases, such as poor general condition, young age, intercurrent disease, and certain questionable changes of the roentgen picture or of the liquor add to the difficulty of reaching a decision. The authors suggest a change from the present system of institutions to the establishment of screening centers from where the children are referred to either treatment or observation hospitals where they will be under the care of a specialized staff equipped with excellent technical facilities.

GLASER, Jerusalem.

TREATMENT OF TUBERCULOUS MENINGITIS AND RESULTS OF FIVE-YEAR EXPERIENCE IN KINDERSPITAL IN ZURICH. E. ROSSI and A. STOCKLI, Helvet. pædiat. acta **8**:451 (Nov.) 1953.

Of 104 children with tuberculous meningitis treated since 1947 in the Children's Hospital, Zurich, the results in 62 are evaluated. Forty-two cases are not considered, for the following reasons: (*a*) follow-up of less than one year, (*b*) lack of bacteriological diagnosis, (*c*) hospital admission after more than one week of treatment, or (*d*) death in the first week.

Of seven children treated with high doses of streptomycin, all died. Of seven children treated with low doses for a short period or treated in short courses with long intervals, five died. Of 48 children treated with low doses of streptomycin combined with sulfones and *p*-aminosalicylic acid (PAS) over a long period, 30 are still alive. Five show severe cerebral sequelae, and two, a mild auditory damage. Ninety per cent have a mild vestibular damage. In three children skeletal tuberculosis developed later.

Transitory complications included paralysis, hydrocephalic crises, psychic disturbances, and disturbances of the autonomic nervous system.

The fatalities were distributed evenly over the first nine months of treatment. The death rate was 52% in the first three years of life and 22% in the older children. The difference is probably due to the difficulty of early diagnosis in infants. The prognosis depends on the stage of the disease in which treatment is started—stage of pure meningitis, stage of sensory and peripheral nerve involvement, and stage of coma. The death rates are equal for meningitis with miliary tuberculosis of the lungs (7 deaths among 21 patients) and without miliary tuberculosis of the lungs (6 deaths among 21 patients). In contrast to this, the prognosis of meningitis occurring during streptomycin treatment of miliary tuberculosis of the lungs is poor (four deaths among six patients).

The values for protein, chlorides, and sugar in the spinal fluid at the start of treatment have no prognostic importance.

The combined treatment with streptomycin and isoniazid was satisfactory in the 18 patients treated so far. This method has the advantage that the necessary period of treatment is shorter, but the experience is not yet long enough (one and a half years) to allow definite conclusions.

FROM THE AUTHORS' SUMMARY.

TREATMENT OF TUBERCULOUS MENINGITIS WITH STREPTOMYCIN, PAS, AND ISONIAZID IN CHILDREN'S HOSPITAL, A. KYRIAKOU, ATHENS. S. CHAROCOPOS and E. INGLESSI, Helvet. pædiat. acta **8**:481 (Nov.) 1953.

The authors report 141 tuberculous meningitis cases which were treated with streptomycin, *p*-aminosalicylic acid (PAS), and isoniazid (INH). There were 72 fatalities, 69 recoveries, and 12 recurrences, of which 5 were fatal. Total mortality was 51.06%. Particularly emphasized are the significance of the disease in early childhood and those cases with miliary involvement and those previously treated with a streptomycin for other tuberculous conditions. The visual

and acoustic disturbances; the endocrine, psychic, kidney, and liver alterations, and the skin manifestations which occur during treatment of tuberculous meningitis are discussed. A general survey of the modern therapy of tuberculous meningitis with streptomycin, PAS, and isoniazid is given.

FROM THE AUTHOR'S SUMMARY.

TUBERCULOUS MENINGITIS TREATED BY THIOSEMICARBAZONE AND STREPTOMYCIN. G. CASCIO and R. PURPURA, Clin. pediat. **35**:135 (March) 1953.

Cures were obtained in the cases of three children, 4, 6, and 8 years old, by the use of thiosemicarbazone (50 to 125 mg. daily), supplemented by 10 mg. of streptomycin intrathecally.

HIGGINS, Boston.

RELATION OF CLINICAL COURSE OF TUBERCULOUS MENINGITIS TO COEXISTING PULMONARY LESIONS IN PATIENTS TREATED IN PEDIATRIC CLINIC IN BOLOGNA. A. DEGLI ESPOSTI, Clin. pediat. **35**:171 (March) 1953.

An analysis has been made of the cases of 167 children with tuberculosis to establish, if possible, a relation between the prognosis in tuberculous meningitis and the coexisting type of pulmonary infection which the child had. Although all cases of tuberculous meningitis are severe and prolonged, some are relatively milder in type and respond to treatment more quickly. Of 80 children with only a simple adenopathy, 48 had mild cases and only 2 died. Of 29 children with tuberculous adenitis, 8 had relatively mild cases and 8 died. Of 23 children with the so-called allergic adenopathy, only 2 had relatively mild cases and 11 died. Of 25 children with pulmonary infiltration, 10 had mild cases and 7 died. Of 27 children with miliary tuberculosis, 8 had mild cases and 5 died. Of three children with tuberculous cavities, all had a prolonged and severe clinical course. It would appear that the prognosis in children with tuberculous meningitis is poorer if there is pulmonary-hilus tuberculosis or the presence of a marked allergic reaction to tuberculin. The prognosis in miliary tuberculosis is good if the miliary processes are not massive.

HIGGINS, Boston.

COMPARISON OF RESULTS OF TUBERCULIN TESTS DONE ON SCHOOL CHILDREN FROM VENICE AND SURROUNDING PROVINCIAL VILLAGES. S. TARONNA and G. M. SANTI, Clin. pediat. **35**:455 (July) 1953.

Tuberculin tests were done on 24,150 school children from the province of Venezia; 2,347 (9.7%) of the tests were positive. This is a definitely lower percentage than had been found in school children from the city of Venice (25%).

X-ray films and physical examinations of the children revealed only 45 cases of tuberculous disease; 39 were of primary and 6 of postprimary tuberculosis.

The incidence of tuberculous infection (number of positive tuberculin tests in the school children) and of tuberculous disease (number of dispensary tuberculosis cases) did not run parallel for the different villages.

HIGGINS, Boston.

THE TREATMENT OF TUBERCULOUS MENINGITIS IN THE PEDIATRIC CLINIC OF BOLOGNA USING STREPTOMYCIN AND ISONIAZID. M. ORLANDELLI and A. DEGLI ESPOSTI, Clin. pediat. **35**:495 (July) 1953.

The routine technique now followed in the treatment of patients with tuberculous meningitis in the pediatric clinic in Bologna is outlined. It consists of intramuscular injections of 10 to 20 mg. per kilogram of body weight of streptomycin, given daily for the first 140 days. Injections of 4 to 6 mg. per kilogram of isonazid are begun on the 45th day, continued for 25 days, omitted for 25 days, and again resumed for 25 days. After 140 days, the isoniazid and the streptomycin injections are alternated over periods of 30 days.

Intrathecal injections of 1 to 2 mg. per kilogram of streptomycin are given daily for 90 days; then 0.5 to 1.0 mg. per kilogram of isoniazid is given daily for 30 days. Then the streptomycin is injected for 30 days and then the isoniazid for 30 days. These medicines are alternated for 30 days, as long as they appear to be indicated by the clinical condition of the patient.

Of the 40 patients treated under this plan, 36 have recovered, 30 of them without sequelae.

HIGGINS, Boston.

CAREFUL SEARCH FOR PRIMARY FOCUS IN TUBERCULOSIS. S. TARONNA, Clin. pediat. **35**:885 (Dec.) 1953.

The author reports that, with rare exceptions, he has been unable to detect roentgenologically the appearance of the primary focus of tuberculosis in children before the hilar enlargement is apparent. Serial x-ray pictures are shown of children with a known time of exposure to tuberculosis; the calcified focus was apparent in later films but could not be detected in the earlier films.

HIGGINS, Boston.

TREATMENT OF CHILDHOOD TUBERCULOSIS WITH ISONIAZID. P. BRUSA and B. CARLETTI, Minerva pediat. **5**:225 (April 15) 1953.

In 1952, in the pediatric clinic of the University of Milan, 51 children were treated for various types of tuberculosis with isoniazid. The daily dose of the drug at first was 3 mg. per kilogram of body weight, and was gradually increased to 10 mg. per kilogram; children with meningitis also received 1 mg. per kilogram of the drug, together with streptomycin, intrathecally. The therapeutic results were very satisfactory. Only two of the children died. The duration of the treatment of children with tuberculous meningitis was definitely shorter than had been the case in those treated by streptomycin alone. In the cases of miliary tuberculosis, isoniazid when given alone was found to be quite as efficacious as when given with streptomycin. Of 27 children showing dense pulmonary shadows with x-rays, good therapeutic results were obtained with 18, while the condition of 7 children was stationary and that of 2 became worse.

HIGGINS, Boston.

TUBERCULOUS PATHOLOGY DURING FIRST THREE YEARS OF LIFE. M. SAGGESE and G. CROCCO, Pediatria **61**:586 (July-Aug.) 1953.

The authors compare the clinical findings in 57 children under 3 years of age having tuberculosis from unknown exposure with the findings in children of the same age but with a known source of infection. A higher percentage of the children with unknown exposure had diffuse tuberculous lesions, and a lower percentage, localized lesions or the allergic type of tuberculosis.

HIGGINS, Boston.

SEDIMENTATION RATE AND ALLERGIC REACTION TO TUBERCULIN IN PATIENTS WITH TUBERCULOSIS BEING TREATED BY THIOSEMICARBAZONE AND STREPTOMYCIN. G. CASCIO and R. PURPURA, Pediatria **61**:607 (July) 1953.

Observations were made on 10 patients with various types of tuberculosis during the course of their treatment with thiosemicarbazone. Some of the patients were also being given streptomycin. A definite fall in the blood sedimentation rate was found in all the patients. The tuberculin reaction usually tended to become less intense, but this was not always the case.

HIGGINS, Boston.

TITER OF ISONIAZID IN THE SPINAL FLUID OF CHILDREN SUFFERING FROM AND RECOVERED FROM TUBERCULOUS MENINGITIS. MARIO VERROTTI and NEVIO BARDELLI, Riv. clin. pediat. **5**:143 (Feb.) 1953.

The authors, after having described the characteristics of the hematoencephalic barrier, point to the alterations it undergoes during the course of various diseases and to the differences existing between integral and affected meninges in relation to the passage of chemical substances existing in the blood.

They also refer to the data concerning isoniazid titration in the spinal fluid of children recovered from tuberculous meningitis after oral and intravenous administration. The titration was effected by a chemical method (iodometrical method) and by a microbiological method. The examination of such data enables the authors to draw the following conclusions: 1. The hemato-encephalic barrier is passed by isoniazid in all cases where inflammatory processes of the leptomeninges exist. 2. The administration of 5 mg. per kilogram of body weight is sufficient to obtain, in the first two to three months of the illness (tuberculous meningitis) an appreciable rate of isoniazid in cerebrospinal fluid. 3. The elimination of the isoniazid from the cerebrospinal fluid is effected rather rapidly between the 3d and the 12th hours after administration.

FROM THE AUTHORS' SUMMARY.

TREATMENT OF TUBERCULOUS MENINGITIS. M. DEL SOLDATO, J. pediat. (Rio de Janeiro) **18**:311 (Sept.) 1953.

The author reviews his experiences during a year of study at the University of Florence. An extensive resumé of the treatment of tuberculous meningitis is presented, with an extensive bibliography.

FROM THE AUTHOR'S SUMMARY.

RELATIONSHIP OF SITES OF BCG VACCINATION AND TUBERCULIN TEST SENSITIVITY. KURT LOTHER, Monatsschr. Kinderh. **101**:317 (Aug.) 1953.

Sixty children who had received BCG vaccination were given intracutaneous old tuberculin tests. The test was performed simultaneously at two sites: (1) 3 cm. from the BCG vaccination scar on the thigh, and (2) at a corresponding area on the other thigh. Tuberculin tests administered near the vaccination site were more strongly positive after 24 hours than those on the opposite thigh, but the difference was much less marked after 48 hours. Maximal reactions occurred more rapidly near the site of BCG vaccination.

Children who had acquired tuberculin sensitivity by natural means had longer-lasting positive reactions than those who had received BCG vaccination, regardless of on which thigh the tuberculin tests had been given. Children who had been vaccinated with BCG vaccine shortly before tuberculin testing showed remarkably rapid tuberculin positivity and acceleration of duration of positive reactions.

HARTENSTEIN, Syracuse, N. Y.

LONG-RANGE PROGNOSIS OF TUBERCULOUS MENINGITIS IN CHILDREN. M. GRAFFAR, P. GILLET, J. JADOT-DECROLY, S. PELC, and O. LEPÈRE, Acta pædiat. belg. **7**:121, 1953.

A total of 302 patients with tuberculous meningitis were treated during the years 1946 to 1950 at the University Clinic of Pediatrics of Brussels. Of the 145 surviving patients, 96 were under 14 years of age at the time of their hospitalization and were discharged as cured of meningitis not later than December, 1950.

A two to six year follow-up study was carried out on these younger patients in 1952—in 20 by correspondents and in 76 by the authors themselves. Vestibular disturbances were found in 88% and acoustic in 23%. (Since January, 1951, the high figure of auditory disturbances has been reduced to 5% by a modification of treatment methods.) Sixteen patients had other neurologic disturbances; 6 showed later tuberculous bone involvement, and in 5 persistent obesity followed the recovery from meningitis.

Changes and disturbances of intellect, character, family adjustment, and school progress were found in many cases and were thoroughly investigated. Electroencephalographic studies of 32 children who showed neither somatic nor mental disturbances revealed 1 abnormal and 3 doubtful tracings; among 16 cases with character disturbances no pathological tracings were found, and among 11 cases with neurologic changes 3 abnormal tracings were discovered.

GLASER, Jerusalem.

ANTIBIOTICS IN TREATMENT OF TUBERCULOSIS IN CHILDREN. A. J. M. MULDER, Maandschr. kindergeneesk. **21**:24 (Jan.) 1953.

The four principal antibiotics against tuberculosis—streptomycin, *p*-aminosalicylic acid (PAS), *p*-acetylaminobenzaldehyde thiosemicarbazone (TBI), and isoniazid—are described. Personal observations are mentioned. The value of streptomycin and PAS is certain. TBI is too toxic

for children. Isoniazid seems very active against acute miliary tuberculosis and meningitis, especially when combined with other antibiotics. In primary tuberculosis, the clinical action of isoniazid seems favorable and the roentgenological action doubtful. In connection with the early appearance of resistance in cavernous tuberculosis, it is necessary to consider the reaction of isoniazid combined with other antibiotics.

FROM THE AUTHOR'S SUMMARY.

ASPECTS AND RESULTS IN TREATMENT OF TUBERCULOUS MENINGITIS. W. VAN ZEBEN, Maandschr. kindergeneesk. **21**:73 (March) 1953.

Conceptions regarding the symptomatology in cases of tuberculous meningitis are reviewed. At the beginning of the illness a toxic lesion of the cerebrum is considered as the most important factor, whereas later on an anatomical damage of the brain stem by the exudate at the base of the brain or by high intracranial pressure is more important. For the estimation of the intracranial pressure at any period of the illness, it is necessary in every case to make a frontal burr hole at the beginning of the illness and to carry out ventricular drainage when this pressure is high.

A survey is given of the results obtained.

It is of primary importance that patients with tuberculous meningitis be treated in a special center.

FROM THE AUTHOR'S SUMMARY.

Diseases of Blood, Heart and Blood Vessels, and Spleen

ANATOMIC VARIATIONS IN TETRALOGY OF FALLOT. T. G. BAFFES, F. R. JOHNSON, W. J. POTTS, and S. GIBSON, Am. Heart J. **46**:657 (Nov.) 1953.

Forty-two specimens showing the tetralogy of Fallot available in the laboratory of the Children's Memorial Hospital, Chicago, were classified into groups with relatively similar infundibular anatomy, with a view to evaluating the relative applicability of intracardiac infundibular resection and the shunt operations to each of these groups.

There were 12 specimens with pulmonary atresia, 4 of them showing a pulmonary arterial segment adequate to have permitted a shunt operation. Of the remaining 30 hearts, which showed infundibular stenosis and patent pulmonary arteries, 22 would probably not have been amenable to intracardiac surgery at this time. Eight hearts, however, showed a type of infundibular deformity in which intracardiac surgery seemed feasible. These comprised 19% of the series.

All hearts with pulmonary valvular stenosis were accompanied by infundibular deformity and, in most instances, revealed associated hypoplastic pulmonary arteries.

Most specimens showed moderate or severe overriding of the aorta.

Eighty-two per cent of this series was comprised of hearts taken from children under 3 years of age. Therefore, these specimens probably represented severer types of the tetralogy of Fallot. Other studies, with findings differing from ours, were done mainly on older children and adults. The difference in ages may account, in part, for the difference in pathologic findings.

FROM THE AUTHORS' SUMMARY.

HEMORRHAGIC DISEASES IN FILIPINO CHILDREN. EUGENE STRANSKY and ELEONORA P. DACANEY, Philippine J. Pediat. **2**:1 (Oct.-Dec.) 1953.

One hundred thirty-six cases of hemorrhagic syndrome were observed and analyzed in children. There were 36 instances of acute leukemia, 24 cases of aplastic anemia. Secondary purpura due to these two diseases is very frequent in the Philippines and has to be considered as a possibility in any case. Furthermore, there were 29 cases of thrombopenic purpura, 30 cases of nonthrombopenic purpura, 7 cases of hemophilia, 3 cases of thrombopenic purpura, and 9 nonclassified cases observed at the same time. The differential diagnosis of these diseases is discussed, with the emphasis on the observation of the retractility of the clot and the tourniquet test. The symptomatology of the hemorrhagic diseases is likewise tabulated and discussed, together with the therapy.

FROM THE AUTHORS' SUMMARY.

PERIARTERITIS NODOSA: REPORT OF TWO CASES WITH AUTOPSY. LEON V. PECACHE and CONCHITA RALUTIN-MANGALINDAN, Philippine J. Pediat. **2**:19 (Oct.-Dec.) 1953.

The very low incidence of periarteritis nodosa is the same here as in other hospitals abroad. In both cases reported, there was intermittent fever, tachycardia, and abdominal and chest pains. In addition, one had low back and iliac pains, headache, and urinary findings, while the other had convulsions. In the case where we had laboratory examinations, there was persistent leucocytosis. The 2 cases are compared to the analysis of 42 cases of periarteritis nodosa done by Keith and Bagentoss. The organs involved, as shown in the histological sections, were almost of the same extent in both cases. This fairly fits in the studies of Gruber of 108 cases.

FROM THE AUTHORS' SUMMARY.

HEAVY METALS (IRON, COPPER, ZINC) IN BLOOD OF THE FETUS AND THE INFANT. B. HAGBERG, S. AXTRUP, and B. BERFENSTAM, Études néo-natal. **2**:81 (June) 1953.

A survey is given of the behavior of iron, copper, and zinc in the blood of the fetus and the infant. For the sake of comparison, some data on the liver content and/or body content of the same metals are included.

FROM THE AUTHORS' SUMMARY.

SERUM IRON LEVELS IN DIFFERENT BLOOD DISEASES: THEIR IMPORTANCE FOR DIFFERENTIAL DIAGNOSIS. E. STRANSKY and C. VICENTE, Ann. pædiat. **180**:163 (March) 1953.

Iron determinations of the blood serum were done in 108 cases. In iron deficiency anemia, especially hookworm anemia, the iron level of the serum was nearly or exactly zero. In aplastic anemias, as well as in infectious anemias, the serum iron level was markedly increased. Whereas in Filipino children the average serum iron level was 30 to 40 γ per 100 cc., the authors found an average of 196 γ per 100 cc. in aplastic anemia and of 163 γ per 100 cc. in infectious anemia. The highest serum iron levels were found in hemolytic anemia, the average being 250 γ per 100 cc. They found high iron levels in congenital heart anomalies, characterized by polyglobulia and cyanosis. In acute leukemia, the average iron level was 178 γ per 100 cc., while in chronic leukemia, as far as could be found, the levels might be normal or high, depending on the stage of the disease. In hemorrhagic diseases, and in case of loss of blood, the serum iron level might be very low immediately after the loss of blood or the acute stage of the hemorrhagic disease, while in later stages the level might be normal. In thrombocytopenic purpura the serum iron level seemed to be higher than normal, most probably as a result of hypersplenism. The problem of hypersplenism with respect to the serum iron levels will be studied later.

FROM THE AUTHORS' SUMMARY.

LEUKEMIA IN CHILDREN TREATED WITH CORTISONE AND AMINOPTERIN. C. GASSER and R. CRAMER, Helvet pædiat. acta **8**:10 (March) 1953.

A precise study was carried out of the action of cortisone and aminopterin in 15 cases of leukemia capable of being followed up, out of 25 patients admitted to the hospital during 1951-1952.

Cortisone produced in eight cases of acute blast cell leukemia a complete bone marrow remission (in one case two successive remissions), while in three such cases remission was only partial. The effect of cortisone was deficient in two cases of promyelocytic leukemia with hiatus and harmful in two cases of myelocytic leukemia without hiatus. Aminopterin was used only as an alternative treatment with cortisone. In a case of promyelocytic leukemia, aminopterin, used after cortisone treatment, caused a total remission, still lasting afer 12 months. In blast cell leukemia aminopterin used after cortisone caused one complete and several partial remissions. Aminopterin had some slight effect on myelocytic leukemia without hiatus, but this form of leukemia reacted much better to x-irradiation of the spleen. The treatment should be chosen, therefore, on the basis of the cytological classification of leukemia. Since the use of cortisone, the average life expectancy for acute blast cell leukemia has been increased twofold (from 100 to 200 days).

Remissions with cortisone not only were frequent and repeatable but also showed a very consistent course. Disappearance of clinical symptoms and pathological cells in the blood during the first week was followed in the second and third weeks by a spontaneous improvement of the anemia without use of blood transfusions, due to a strong increase of erythropoiesis associated with the disappearance of granulocytopenia and thrombocytopenia in the bone marrow and blood.

Complementary therapy included only continuous treatment with antibiotics, vitamins B and C, and a diet poor in salt to avoid water retention. The complications routinely caused by cortisone were a reversible Cushing-type adiposity and a slight elevation in blood pressure. Aminopterin caused a hemorrhagic diathesis, due to a disturbance of coagulation, which could not be completely prevented with the citrovorum factor. Worth mentioning are the cytological particularities, such as phagocytosis of erythroblasts and erythrocytes in the bone marrow during aminopterin or cortisone therapy, or megaloblastic reaction and accumulation of basophilic pigment with aminopterin.

In contrast to aminopterin, which has an inhibitive action on all the elements of the bone marrow, cortisone has a specific antianabolic action on the leukemic cells. We observed a sharp decrease of mitosis in blast cell leukemia and in one case of promyelocytic leukemia. The complete normalization of all the cells in bone marrow can be explained either as a consequence of a change in metabolic equilibrium favoring a normal hematopoiesis or as a direct specific stimulation of the bone marrow. In one case of monomyelocytic leukemia, which did not respond by remission to either cortisone or aminopterin, a morphologic change of the type of leukemic cell was found. Our autopsy findings confirm the view based on animal experiments, that the adrenals react differently to aminopterin and to cortisone, in that an adrenal atrophy was observed only in cases treated with cortisone alone. FROM THE AUTHORS' SUMMARY.

THE TREATMENT OF LEUKEMIA IN CHILDREN WITH CORTICOTROPIN (ACTH) AND CORTISONE WITH PARTICULAR REGARD TO THE INTRADERMIC USE OF CORTICOTROPIN (ACTH). E. BOTTONE and M. BISCIONI, Arch. ital. pediat. puericolt. **16**:181, 1953.

The authors, after summarizing the literature regarding corticotropin (ACTH) and cortisone therapy in leukemia, describe and discuss five cases of acute leukemia in children who have been given these hormones in association with antibiotics, blood transfusions, etc. Results reported by the authors, which did not differ very much from those obtained by preceding observers, can be summarized as follows: (1) one complete clinical and hematologic response, (2) three clinical remissions, with partial hematologic response, and (3) one negative result.

The average survival of the children treated in this way was 6 months (maximum, 10 months, minimum, 2 months).

Attention has been particularly devoted to the use of microdoses of corticotropin given by intradermal injection. This method, first tried by the authors in the treatment of the leukemias, has obtained effects superior to those reported by other investigators wih normal doses of the hormone.

FROM THE AUTHORS' SUMMARY.

RIGHT ANTERIOR OBLIQUE POSITION FOR ANGIOCARDIOGRAPHIC STUDIES. A. CASTELLANOS and OTTO GARCÍA, Arch. med. inf. **22**:155 (July-Sept.) 1953.

We have used the right anterior oblique position in angiocardiographic studies on both sides of the angiocardiograms in the most frequent cardiac malformations that we see clinically.

We pointed out that this position gives us an opportunity of seeing the image in cases of patent ductus arteriosus, affording the special finding of a pathognomonic image and enlarged left auricle in the cases of a great arteriovenous shunt.

In the other cardiac malformations the right anterior oblique view has no advantages over the anteroposterior and the left anterior oblique.

In a future paper, we shall evaluate the right anterior oblique position in cases of patent ductus arteriosus.

FROM THE AUTHORS' SUMMARY.

CASE OF THROMBOPENIA AS A RESULT OF ADMINISTRATION OF ISONIAZID. R. L. BAART DE LA FAILLE and M. C. VERLOOP, Nederl. tijdschr. geneesk. **97**:545 (Feb. 28) 1953.

A case of pulmonary tuberculosis is described in which thrombocytopenic purpura occurred as a result of treatment with isoniazid. The blood picture returned to normal after discontinuation of treatment.

VAN CREVELD, Amsterdam.

BILIRUBIN IN THE BLOOD. L. SCHALM and M. J. SCHULTE, Nederl. tijdschr. geneesk. **97**:1013 (April 18) 1953.

With the aid of a photoelectric colorimeter, distinction was made between rapidly and slowly reacting bilirubin. The reaction rate was expressed in the 10-minute percentage of diazotization. The quantities of rapidly and slowly reacting bilirubin, reactions which in a large number of cases occurred simultaneously in the blood, can be derived from this percentage by a simple method. The existence of these mixtures explains a number of clinical findings hitherto difficult to interpret. Animal experiments and observations made in human pathology show that rapidly reacting bilirubin in the blood is suggestive of a morbid condition. A physiopathological definition of various forms of jaundice is given.

VAN CREVELD, Amsterdam.

THALASSEMIA (COOLEY'S ANEMIA) IN A DUTCH FAMILY. S. DE VRIES and R. A. VAN VALKENBURG, Nederl. tijdschr. geneesk. **97**:2789 (Oct. 24) 1953.

This is a report on a Dutch family—the first to be described in the Netherlands—with thalassemia minor and thalassemia minima. The characteristic anomalies were demonstrable in nine relatives.

VAN CREVELD, Amsterdam.

PLANIGRAPHIC EXAMINATION OF DESCENDING PART OF AORTA. J. B. VERHEY, Nederl. tijdschr. geneesk. **97**:2836 (Oct. 31) 1953.

The technique of sectional planigraphic examination of the descending aorta is described. Sometimes good results are obtained without the help of injection of contrast media. Focus and film motion are linear and verticle with this method while the patient is recumbent. Case reports are given of coarctation and aneurysm of the aorta.

VAN CREVELD, Amsterdam.

Miscellaneous

WHAT IS NEW IN ADOPTION. DONALD G. TOLLEFSON, California Med. **78**:222 (March) 1953.

Adoptions arranged through adoption agencies are on the increase because there are more agencies. The Citizens Committee on Adoption of Children in California has concluded that there are very few adoptable children under care in orphanages. Fifty per cent of physicians would prefer agency adoptions, but only 24% actually refer both expectant mothers needing such services and couples wishing to adopt infants to such agencies. The program in this field of social welfare should be child-centered, and physicians should seek and give cooperation to such agencies.

PRYOR, Redwood City, Calif.

COMPARISON OF SERUM LEVELS FOLLOWING THE ADMINISTRATION OF ORAL AND PARENTERAL PREPARATIONS OF PENICILLIN TO INFANTS AND CHILDREN OF VARIOUS AGE GROUPS. NANCY N. HUANG and ROBERT H. HIGH, J. Pediat. **42**:657 (June) 1953.

Huang and High say that oral administration of penicillin G in doses of 10,000 units per pound (0.5 kg.) of body weight every 12 hours should be effective in the treatment of infections by susceptible organisms in infants. In children over the age of 2 years the same dose should be given at 6-hour intervals.

Intramuscular penicillin procaine was given in doses of 10,000 units per pound of body weight. Although it produced very high initial serum levels, these levels declined so that 6-hour levels

were comparable to those observed after the oral administration of penicillin in all age groups except the youngest newborn and prematures. However, the authors say that intramuscular penicillin is indicated in moderately severe infections caused by penicillin-susceptible organisms.

MACDONALD, Pittsburgh.

HOMEOSTATIC LIMITS TO SAFE PARENTERAL FLUID THERAPY. NATHAN B. TALBOT, JOHN D. CRAWFORD, and ALLAN M. BUTLER, New England J. Med. **248**:1100 (June 25) 1953.

This article deals with the possibility of so designing parenteral fluid therapy that patients may make full use of their homeostatic mechanisms during the critical period when the physician's order, rather than instinct, prescribes water and solute intake.

The homeostatic mechanisms pertinent to the water, sodium, potassium, phosphate and dextrose needs of patients whose illness prescribes intravenous infusion therapy are discussed. An attempt is made to indicate in approximate terms both the least amount of each substance needed to correct or prevent abnormal body deficits and the greatest amount that can be administered without upsetting concentrations or volumes of body fluids to a pathologic degree. The manner in which the organism can retain or reject intermediate amounts in accordance with its best interests is then discussed and exemplified. All results are expressed on a basis of square meter of body surface, since this makes them applicable to patients of all ages.

WHEELOCK, Denver.

News and Comment

ANNOUNCEMENTS

Convention of National Society for Crippled Children and Adults.—The 31st National Convention of the National Society for Crippled Children and Adults will be held at Hotel Statler, Boston, from Nov. 2 to 6, 1954.

PERSONAL

Prof. Ernst Freudenberg.—On June 24, 1954, Prof. Ernst Freudenberg, director of the Children's Hospital in Basel, Switzerland, celebrated his 70th birthday. His retirement will take place Oct. 1. It is fitting that his American friends and pediatric colleagues express their esteem for a great scholar, teacher, investigator, and pediatrician and wish for him many more years of health and productivity.

Ernst Freudenberg was born in 1884, at Weinheim, Baden, Germany. He studied medicine in Leipzig and in Munich, receiving his doctor's degree in the latter city in 1910. His scientific career began immediately in the Munich Kinderklinik under Professor Ibrahim, where he remained for two years. There followed periods in Strassburg and Heidelberg, where he came under the influence of Professors Hoffmeister, Spiro, and Moro. In 1922 he was called to the professorship of pediatrics at Marburg an der Lahn. Here he came to be regarded with both affection and esteem as evidenced by the fact that he was elected dean of the medical faculty by his colleagues. Political events for which he could have no sympathy forced his resignation in 1937. A year later following the retirement of Professor Wieland he moved to the position he now holds in Basel.

Freudenberg's life has been one of continued productivity. His personal writings in the form of scientific articles published in pediatric and biochemical journals, contributions to standard textbooks, and monographs number more than 140. Much more has come from pupils stimulated by his imagination and ideas. Perhaps he is best known for his many publications on rickets and tetany and for his monograph, printed in 1929, on the physiology and pathology of digestion in infancy. For this monograph he was awarded the Otto Heubner prize. He will also be known for having accepted in Basel the editorship of the world's oldest pediatric journal, *Jahrbuch für Kinderheilkunde*. Under his direction, the journal has become international in scope and is published in three languages, German, English, and French, under a new title *Annales Pædiatrici*.

Sometime in the autumn of 1954 there will appear a memorial volume in honor of Ernst Freudenberg. Again, three languages will be used in a text of more than 800 pages. In English the title of the book will be "Modern Problems in Pediatrics." Contributions will come from investigators and physicians in many different countries, a number being from the United States of America.

The writer of this brief biographic note experienced four unforgettable months in 1931 when he visited Freudenberg's department in Marburg. Recollections of a man of great wisdom will always be associated with memories of kindness, patience and thoughtfulness for the needs of others. He will always occupy a special niche in a personal hall of heroes.

Books

Eleven Blue Men and Other Narratives of Medical Detection. By Berton Roueché. Price, $3.50. Pp. 215. Little, Brown & Company, 34 Beacon St., Boston 6, 1954.

The title of this book keeps one curious until he reads that 11 sick men, all with a blue color, entered a hospital within an hour or two. The cause of the color was sodium nitrite, accidentally used instead of table salt.

Eleven other cases are discussed. These include trichinosis, gout, an outbreak of typhoid, a rare rickettsial occurrence, smallpox, leprosy, tetanus in drug addicts caused by "cutting" heroin for resale, botulism, the illnesses caused by the smog or fog in Pennsylvania, and a discussion of antibiotics.

Each case was obscured by circumstances that required acute detective work by both diagnostician and research men to locate the source and cause of the infection.

The author listened to the accounts of the doctors and investigators and has retold their story as only a superb writer can do. With cases like leprosy, typhoid, and ricketts, he inserts the history of the disease and its treatment in an extremely interesting way.

The book is an enjoyable and educative presentation of problems that any doctor may encounter. The individual chapters were first published as articles in *The New Yorker*. They were written for the general public, but the more of medicine one knows, the more he will enjoy reading this book.

A Synopsis of Children's Diseases. By John Rendle-Short. Price, $7. Pp. 608, with 7 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1954.

At intervals, in the announcements of new medical books, there appear synopsis types of books embracing general medicine and most of the specialties. These have their merits if they are not taken too seriously by the neophyte in medicine.

This book is such a compendium of the diseases of children, written in outline form with short concise statements embellishing the form of presentation. In its 608 pages there are 21 sections which denote diseases in systems, such as "Diseases of the Cardiovascular System" and "Diseases of the Respiratory System." These are further divided into 164 chapters representing each of the entities of the sections. Three of the unusual sections are those on "The Healthy Child," "The Neonatal Period," and "Accidents in Childhood." The material is excellently indexed, as such a book must be, to improve its usefulness. There is the inevitable appendix, which contains drug dosages appropriate for children, and a second portion giving the normal biochemical values, the normal blood cytology values, and the cerebrospinal fluid values. There is also included in the appendix a series of special tests pertaining to specific investigations peculiar to children. All of the material is up to date, and each disease entity is designated as rare or common, for the elucidation of the less-experienced reader in clinical pediatrics.

As the author pointedly states in the preface, this book should not take the place of standard textbooks on the subject of pediatrics. It is written as a help for those who are preparing for comprehensive examinations in pediatrics, as well as to be a reference book for pediatric house physicians and for general practitioners. Some minds are receptive to the outline form of information and would find the book invaluable in preparing for a specific examination. Others would be dismayed if faced with retaining in their minds the mass of data here presented.

The book is designed to assemble in one place relevant facts for easy reference and rapid orientation. To this end it fulfills is purpose. Any seasoned pediatrician would look upon it as an interesting handbook to refresh his memory on the more unusual entities he might meet and would be stimulated to read further in more extensive discussions on the variations of the specific disease problems suggested by the outline. A few references as to authorities are given in footnotes, but no bibliography is contained to lend authority to the contents of this book.

One admires the tremendous amount of effort, clinical skill, and ultimate knowledge that is involved in the authorship of such a book, and the editing of the great mass of material is also a Herculean feat. The book is recommended by this reviewer if the values and limitations expressed above are kept in mind.

Directory of Pediatric Societies *

INTERNATIONAL

International Union for Child Welfare

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 16 rue du Mont Blanc, Geneva, Switzerland.

IV° Congreso Pan-Americano de Pediatria

President: Dr. Leonel Gonzaga.
General Secretary: Dr. Adamastor Barbosa.
Secretariat: Rua Dias da Rocha 25, ap. 602, Copacabana, Rio de Janeiro.
Place: Rio de Janeiro. Time: 1954.

IV° Congreso Sudamericano de Pediatria, Confederacion Sudamericano de Sociedades de Pediatria

President: Prof. Carlos Prado.
Vice-President: Dr. Marcelo Garcia.
General Secretary: Dr. Alvaro Aguiar.
Place: Avenida mem de Sá 197, Rio de Janeiro. Time: 1954.

FOREIGN

Academy of Medicine, Toronto, Section of Paediatrics

Chairman: Dr. Bernard Laski, Toronto.
Secretary: Dr. Crawford Anglin, Toronto.
Place: Academy of Medicine.

Asociación de Pediatras Españoles

President: Dr. Rafael Ramos Fernández.
Vice-Presidents: Dr. Juan Bosch Marín and Dr. Ciriaco Laguna.
Secretary-General: Dr. Luis Navas Migueloa.
Treasurer: Dr. Angel Ballabriga.

Australian Paediatric Association

President: Dr. P. A. Earnshaw, Ballow Chambers, Wickham Terrace, Brisbane. B17.
Honorary Secretary-Treasurer: Dr. D. C. Jackson, 217 Wickham Terrace, Brisbane. B17.
Place: Canberra. Time: Yearly in April.

British Paediatric Association

President: Prof. J. Smellie.
Secretary: Prof. Alan Moncrieff, Institute of Child Health, The Hospital for Sick Children, Great Ormond St., W.C. 1, London.
Place: Windermere. Time: Between Easter and Whitsunday.

Canadian Paediatric Society

President: Dr. G. R. Gayman, 710 Seymour St., Vancouver 2, B. C.
Secretary-Treasurer: Dr. J. C. Rathbun, 526 Waterloo St., London, Ont.

Danish Pediatric Society

President: Dr. A. Rothe-Meyer, Children's Hospital, Füglebakken, Copenhagen F.
Secretary: Dr. E. Winge Flensborg, Children's Hospital, Martinsvej, Copenhagen V.
Place: Different hospitals. Time: First Wednesday of every month.

Departamento de Pediatria da Associação Paulista de Medicina

President: Dr. J. Leme da Fonseca.
Secretary: Dr. Joaquim da Costa Marques.

Departamento de Puericultura e Pediatria da Associação Medica do Parana

President: Dr. Haroldo Beltrao.
Secretary: Dr. Mucio de Ãbreu Neto.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Deutsche Gesellschaft für Kinderheilkunde

President: Prof. Dr. med. O. Bossert, Städtische Kinderklinik, Essen.
Secretary: Prof. Dr. med. Jochims, Städtische Kinderklinik, Lübeck.
Place: Essen. Time: September, 1954.

Hellenic Society of Pediatrics

President: Dr. Spiros Charocopos, Alexandras Ave. 1, Athens.
Secretary: Dr. Nikas Zervos.
Place: Amphitheater, Medical School of the University of Athens. Time: Once a month.

Melbourne Paediatric Society

President: Dr. H. McLorinan.
Honorary Secretary: Dr. John H. Colebatch, 12 Collins St., Melbourne.
Place: Royal Children's Hospital, Melbourne. Time: Once monthly, February to December.

Nederlandse Vereeniging voor Kindergeneeskunde

President: Dr. G. J. Huët, 39 Brediusweg, Bussum.
Secretary: Dr. H. Reerink, % Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

Norsk Pediatrisk Selskap

President: Dr. Roald Rinvik, Children's Department, Ullevål Hospital, Oslo.
Secretary: Dr. Bjarne Andersen, Children's Department, Ullevål Hospital, Oslo.
Time: Friday, six times a year.

Pediatric Society of New Zealand

President: Dr. Edward J. Cronin, Power Board Bldg., Queen St., Auckland.
Secretary: Dr. J. D. Matthews, 104 Symonds St., Auckland.

Philippine Pediatric Society

President: Dr. Renato Ma. Guerrero.
Secretary: Dr. Felix A. Estrada.
Place: Santo Tomas University Hospital and other pediatric centers. Time: Every two months.

Royal Society of Medicine, Section of Paediatrics

President: Dr. C. T. Potter.
Honorary Secretaries: Dr. A. P. Norman and Ursula James, M.R.C.P.
Sectional Editor: Dr. D. MacCarthy.
Place: 1 Wimpole St., London W.1 (Correspondence for these honorary officers should be sent to this address). Time: Fourth Friday of each month, 4:15 p.m.

Schweizerische Gesellschaft für Pädiatrie

President: P. D. Dr. F. Bamatter, St.-Léger 8, Genève.
Secretary: Dr. M. Nicod, Place Bel-Air 2, Lausanne.

Sociedad Argentinade Pediatrie

President: Dr. Rudolfo Kreutzer.
Secretary: Dr. Luis M. Cucullu.
Place: Sante Fè 1178, Buenos Aires.

Sociedad Boliviano de Pediatria

President: Dr. Carlos Daza Meruvia.
Secretary: Dr. Cecilio Abela Deheza.
Place: S. C. I. S. P. Bldg. Time: Every Thursday.

Sociedade Brasiliera de Pediatria

For officers, see IV° Congreso Sudamericano de Pediatria, above.

Sociedad Chihuahuense de Pediatría

President: Dr. Alfonso Ruiz Escalona.
Secretary: Dr. Armando G. Herrera.
Place: Hospital Infantil del Estado, Chihuahua, Chih., Mexico.

Sociedad Chilena de Pediatria

President: Prof. Dr. Raúl Gantes A.
Secretary-General: Dr. Edmundo Cardemil.
Place: Medical Society, Merced 565, Santiago.

Sociedad Colombiana de Pediatria

President: Dr. Jorge Camacho Gamba.
Vice-President: Dr. Antonio Alvarez Riaño.
Secretary: Dr. Hernando Vanegas A.
Treasurer: Dr. Efrain Perry Villate.

Sociedad Cubana de Pediatria

President: Prof. Agustin Castellanos y Gonzales.
Secretary: Dr. Carlos Hernandez Miyares, Apartado 2430, Habana.
Place: Catedra de Clinica Infantil Hospital Nuestra Senora de las Mercedes and Hospital Municipal de Infancia, Habana. Time: 9 p.m., last Wednesday of every month.

Sociedad de Pediatría de Concepción (Chile)

President: Dr. Daniel Campos, Hospital Clínico Regional, Concepción.
Secretary: Dr. Obdulia Jiménez, Hospital Clínico Regional, Concepción.
Place: Hospital Clinico Reginal Concepción. Time: 7:30 p.m., second Tuesday of every month, April to December, inclusive.

Sociedad de Pediatria del Litord

President: Dr. Raul Bruera.
Vice-President: Dr. Isidoro Slullitel.
Secretary-General: Dr. Elsa Galimany.

Sociedad de Pediatria y Puericultura del Atlantico

President: Dr. Atilio Marino.
Vice-President: Dr. Helena Uribe de Jimenez.
Secretary-Treasurer: Dr. Hernando Barrios-Angulo.

Sociedade de Pediatria da Bahia

President: Dr. Elysio Pereira de Atbayde.
Secretary: Dr. Eliezer Audiface.

Sociedade de Pediatria de Pernambuco

President: Dr. Antonio Aureliano.
Secretary: Dr. Claudia Figueiredo.

Sociedade de Pediatria do Rio Grande do Sul

President: Dr. Francisco Talaia de Moura.
Secretary: Dr. Enio Pilla.

Sociedade de Puericultura e Pediatria do Maranbão

President: Dr. Odorico Amaral de Mattos.
Secretary: Dr. Joao Mohana.

Sociedade Mineira de Pediatria

President: Dr. Agostinho Fernandes.
Secretary: Dr. Celio Marques Scotti.

SOCIEDADE PORTUGESA DE PEDIATRIA

President: Prof. Dr. Lucio de Almeida.
Vice-President: Dr. Cordeiro Ferreira.
Secretary-General: Prof. Dr. Carlos Salazar de Sousa.
Treasurer: Dr. Mario Cordeiro.
Place: Clinica pediatrica do Hospital D. Estefania, Lisbon. Time: Monthly.

SOCIEDAD URUGUAYA DE PEDIATRIA

President: Dr. Euclides Peluffo.
Secretary: Dr. Ruben Gorlero Bacigalupi.
Place: Av. Agraciada 1464, piso 13, Montevideo.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRÍA

President: Dr. H. Arroyo Parejo.
Vice-President: Dr. Manuel M. Lander.
Secretary: Dr. Guillermo Tovar E., P. O. Box 3122, Caracas.
Treasurer: Dr. Carlos Lares Compos.
Place: Hospital Municipal de Niños "J. M. de los Ríos," Caracas. Time: Once a month.

SOCIEDAD YUCATECA DE PEDIATRIA

President: Dr. Humberto Perez Concha.
Secretary: Dr. Prudencio Ruiz Salazar.
Treasurer: Dr. Jorge Antiveros Andrade.

LA SOCIÉTÉ DE PÉDIATRIE DE MONTRÉAL

President: Dr. Henri Charbonneau, 3095 Sherbrooke, Montréal.
Secretary: Dr. Edmond Baril, 301 Carré St-Louis, Apt. 1, Montréal.
Time: Second Thursday of each month.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Prof. Jean Cathala, 45 rue Scheffer, Paris XVI.
Secretary: Prof. Maurice Lamy, 94 rue de Varenne, Paris VII.
Place: Hôpital des Enfants Malades, 149 rue de Sèvres, Paris XV. Time: 4 p.m., third Tuesday of each month.

SOCIÉTÉ DE PÉDIATRIE DE QUÉBEC

President: Dr. Roland Thibaudeau, 203 des Erables, Québec.
Secretary: Dr. Euclide Dechêne, 312 du Roi, Québec.
Place: Quebec. Time: May and November.

SOUTH AFRICAN PAEDIATRIC ASSOCIATION

Chairman: Dr. Seymour Heymann, 804 Medical Centre, Jeppe St. Johannesburg.
Honorary Secretary-Treasurer: Dr. I. Kessel, Transvaal Memorial Hospital for Children, Milner Park, Johannesburg.

SWEDISH ASSOCIATION OF PEDIATRICS

President: Prof. Sture Siwe, Lund.
Secretary: Dr. Karl-Axel Melin, Färjestadsvägen 16, Bromma.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Docent Urban Hjarne, Stockholm.
Secretary: Dr. M. d'Avignon, Pediatric Clinic, Karolinska Sjukhuset, Stockholm 60.
Place: Swedish Medical Society, Klara Östra Kyrkogata 10, Stockholm, and Pediatric Clinic, Uppsala. Time: Second Friday of each month, except summer.

UNITED STATES

National

AMERICAN MEDICAL ASSOCIATION, SECTION ON PEDIATRICS

Chairman: Dr. William H. Schmidt, 136 S. 16th St., Philadelphia 2.
Vice-Chairman: Dr. Frances Baker, 1 Tilton Ave., San Mateo, Calif.
Secretary: Dr. Walter J. Zeiter, 2020 E. 93d St., Cleveland 6.

American Academy of Pediatrics

President: Dr. Roger L. J. Kennedy, 102 2d Ave., S. W., Rochester, Minn.
Vice-President: Dr. Crawford Bost, 115 Terrace Dr., San Francisco 27.
Executive Secretary: Dr. E. H. Christopherson, 636 Church St., Evanston, Ill.
Treasurer: Dr. Edgar E. Martmer.

Society for Pediatric Research

President: Dr. Russell Blattner.
Vice-President: Dr. Harold E. Harrison.
Secretary-Treasurer: Dr. Sydney S. Gellis, Boston.

The American Pediatric Society

President: Dr. Rustin McIntosh.
Vice-President: Dr. Wilburt C. Davison.
Secretary-Treasurer: Dr. Aims C. McGuinness.

Sectional

Intermountain Pediatric Society

President: Dr. John T. Mason.
Secretary: Dr. Stanley R. Child.
Place: Ambassador Athletic Club, Salt Lake City. Time: 7 p.m.

New England Pediatric Society

President: Dr. Reuben C. Bates, 122 Waterman St., Providence, R. I.
Vice-President (President-Elect): Dr. Louis K. Diamond, 300 Longwood Ave., Boston.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Place: Boston, except Spring meeting. Time: Wednesdays, four times a year.

North Pacific Pediatric Society

President: Dr. Carl Ashley, 2455 N. W. Marshall St., Portland, Ore.
Secretary-Treasurer: Dr. S. Gorham Babson, 1107 S. W. 13th St., Portland, Ore

Northwestern Pediatric Society

President: Dr. F. G. Hedenstrom, 420 Lowry Medical Arts Bldg., St. Paul.
Secretary: Dr. Charles L. Steinberg, 1118 Lowry Medical Arts Bldg., St. Paul.
Place: Minneapolis; St. Paul; Duluth, Minn., and Rochester, Minn. Time: January, April, July, and October.

Rocky Mountain Pediatric Society

President: Dr. John Lichty, Pediatric Department, Colorado General Hospital, 4200 E. 9th Ave., Denver.
Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.
Place: Announced by mail. Time: Monthly dinner meetings, October to June.

Southwestern Pediatric Society

President: Dr. Clement J. Molony, 416 N. Bedford Dr., Beverly Hills, Calif.
Secretary: Dr. Carl A. Erickson, 960 E. Green St., Pasadena, Calif.
Place: Jonathan Club of Los Angeles. Time: 6:30 p.m., second Wednesday in January, March, May, September, and November.

Western Society for Pediatric Research

President: Dr. John Anderson.
Vice-President: Dr. Robert Aldrich.
Secretary-Treasurer: Dr. Forrest Adams.

State

Alabama Pediatric Society

President: Dr. David B. Monsky, 748 Adams St., Montgomery 5.
Secretary: Dr. Alice H. Pye, 305 Church St., Montgomery.
Place: Montgomery.

Arizona Pediatric Society

President: Dr. Henry E. Running.
Secretary: Dr. William F. Schaffman.
Time: On Call.

California Medical Association, Section on Pediatrics

Chairman: Dr. Joseph W. St. Geme, 511 S. Bonnie Brae, Los Angeles 5.
Secretary: Dr. Alvin H. Jacobs, 2201 Webster St., San Francisco 15.
Assistant Secretary: Dr. Clement J. Molony, 416 N. Bedford Dr., Beverly Hills.

Florida State Pediatric Society

President: Dr. Charlotte C. Maguire, 1413 Kuhl Ave., Maguire Bldg., Orlando.
Secretary-Treasurer: Dr. Wesley S. Nock, 273 Alhambra Circle, Coral Gables.

Georgia Pediatric Society

President: Dr. John A. Simpson, Athens.
Secretary: Dr. J. Harry Lange, 490 Peachtree St., Atlanta.
Place: Savannah. Time: At time of annual state meeting.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Louis Spekter, Division of Crippled Children, Department of Health, State of Connecticut, Hartford.
Secretary: Dr. Frank E. Roth, 179 Allyn St., Hartford.
Time: With the Connecticut State Medical Society in the spring, with the Connecticut State Clinical Congress in the fall; winter meeting usually in December.

Illinois State Medical Society, Section on Pediatrics

Chairman: Howard R. Miller, 418 Jefferson Bldg., Peoria 2.
Secretary: Harry H. Boyle, 2376 E. 71st St., Chicago 49.

Indiana State Pediatric Society

President: Dr. Harold D. Lynch, Evansville.
Secretary: Dr. L. T. Meiks, Indianapolis.

Iowa Pediatric Society

President: Dr. P. E. Gibson, 1503 Brady St., Davenport.
Vice-President: Dr. Arlan F. Harrington, 924 M. N. B. Bldg., Cedar Rapids.
Secretary-Treasurer: Dr. Ralph E. Dyson, 3200 University Ave., Des Moines.
Place: Spring meeting in conjunction with the Iowa State Medical Society meeting. Fall meeting in Sept., at University Hospital, Pediatric Dept., Iowa City.

Kentucky Pediatric Society

President: Dr. Margaret Limper, Louisville.
Secretary-Treasurer: Dr. Selby V. Love, Louisville.
Place: Louisville. Time: Spring.

Louisiana State Pediatric Society

President: Dr. Jack E. Strange, 3439 Prytania, New Orleans.
Vice-President: Dr. Charles E. Anderson, 1560 Line, Shreveport.
Secretary: Dr. Joseph M. Perret Jr., 2329 S. Carrollton, New Orleans.
Treasurer: Dr. William C. Rivenbark, 1448 Louisiana Ave., New Orleans.
Place: New Orleans. Time: May.

Massachusetts Hospital Association

President: Dr. Philip D. Bonnet, Administrator, Massachusetts Memorial Hospitals, Boston.
Executive Secretary: Henry G. Brickman, 14 Somerset St., Boston 8.

Michigan State Medical Society, Pediatric Section

President: Dr. Horace L. French, 301 Seymour Ave., Lansing.
Secretary: Dr. Park S. Bradshaw, 1014 Jefferson St., Muskegon.

Montana Pediatric Society

President: Dr. Orville M. Moore, 555 Fuller Ave., Helena.
Secretary: Dr. Joseph W. Brinkley, 410 Central Ave., Great Falls.
Place: Variable. Time: Spring and fall.

Nebraska Pediatric Society

President: Dr. Michael Crofoot.
Vice-President: Dr. Donald C. Nilsson.
Secretary-Treasurer: Dr. A. J. Lombardo, 401 Aquila Ct., Omaha.
Place: Children's Memorial Hospital. Time: 6 p.m., dinner, third Thursday of each month.

New Hampshire Pediatric Society

President: Dr. Margaret R. Reynolds, Windy Row, Petersborough.
Secretary: Dr. Wm. D. Penhale, 1 South St., Concord.
Place: Alternately Concord, Hanover, Laconia, and Manchester. Time: Four times a year.

New Mexico Pediatric Society

President: Dr. M. K. Wylder, Suite 14, Medical Arts Sq., Albuquerque.
Secretary: Dr. Ly Werner, Suite 25, Medical Arts Sq., Albuquerque.
Place: Variable. Time: Every two or three months.

North Carolina Pediatric Society

President: Dr. Robert A. Moore, 1505 Elizabeth Ave., Charlotte 4.
Secretary-Treasurer: Dr. Fred R. Cochran, 1361 E. Morehead St.
Place: Roaring Gap and Chapel Hill. Time: Sept. 12 and Oct. 30, respectively.

South Carolina Pediatric Society

President: Dr. Walter Moore Hart, 117 W. Cheves St., Florence.
Secretary: Dr. John R. Paul Jr., 82 Rutledge Ave., Charleston.
Place: Columbia, S. C. Time: Second Monday and Tuesday in September.

Tennessee Pediatric Society

President: Dr. O. L. Von Canon, 846 McCallie Ave., Chattanooga.
Secretary: Dr. Oliver W. Hill, 4807 Newcom Ave., Knoxville.

Texas Pediatric Society

President: Dr. Robert L. Moore, Dallas.
President-Elect: Dr. M. C. Carlisle, Waco.
Secretary: Dr. James N. Walker, Fort Worth.
Treasurer: Dr. Jack M. Woodall, Big Springs.

Virginia Pediatric Society

President: Dr. T. J. Humphries, Roanoke.
Vice-President: Dr. F. R. Hopkins, Lynchburg.
Secretary-Treasurer: Dr. A. P. Booker, Charlottesville.

WISCONSIN STATE MEDICAL SOCIETY, SECTION OF PEDIATRICS

Chairman: Dr. E. H. Pawsat, Fond du Lac.
Vice-Chairman: Dr. Samuel E. Kohn, Milwaukee.
Secretary: Dr. J. R. Schroder, Janesville.
Delegate: Dr. K. J. Winters, Wauwatosa.
Alternate Delegate: Dr. F. Mellencamp, Milwaukee.

Local

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. C. T. J. Dodge, 15457 Euclid Ave., Cleveland 12.
Secretary: Dr. Beulah Wells, 10515 Carnegie Ave., Cleveland 6.
Place: Allen Memorial Medical Library. Time: 8:15 p.m., October, December, February, and March.

AKRON PEDIATRIC SOCIETY

President: Dr. Joseph M. Ulrich.
Vice-President: Dr. Lewis E. Rector.
Secretary-Treasurer: Dr. Max E. Griffin.
Time: Quarterly.

BALTIMORE CITY MEDICAL SOCIETY, PEDIATRIC SECTION

President: Dr. Wilson Grubb, 4 E. 33d St., Baltimore 18.
Secretary: Dr. Gibson J. Wells, 3101 St. Paul St., Baltimore 18.
Place: 1211 Cathedral St., Baltimore 1. Time: 8:30 p.m., second Tuesday in November, January, and March.

BRONX PEDIATRIC SOCIETY

President: Dr. M. H. Grand, 1749 Grand Concourse, New York.
Secretary: Dr. Charles T. Fried, 1220 Grand Concourse, New York.
Place: Morrisania City Hospital. Time: 8:30 p.m., second Wednesday of each month, except June, July, August, and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Stanley S. Lamm, 20 Plaza St., Brooklyn.
Secretary: Dr. Henry Cohen, 1761 E. 19th St., Brooklyn.
Place: Granada Hotel, Brooklyn. Time: 8:45 p.m., fourth Wednesday of February, March, April, October, and November.

BUFFALO PEDIATRIC SOCIETY

President: Dr. Douglas P. Arnold.
Secretary: Dr. Richard A. Downey.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p.m., first Monday of each month, September to June.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. Frank Williams, 58 Swan St. S., Albany.
Secretary: Dr. Fred W. Bush, 325 Park Ave., Rochester.
Place: Various cities in New York State; fall meeting jointly with Upper New York State Academy of Pediatrics. Time: Third Tuesday of April and October.

CENTRAL OHIO PEDIATRIC SOCIETY

President: Dr. O. W. Hosterman, 350 East Broad St., Columbus 15.
Secretary-Treasurer: Dr. John Riepenhoff, 2998 Sullivant Ave., Columbus.
Place: As announced. Time: Third Wednesday of September, November, January, March and May.

Chicago Pediatric Society

President: Dr. Eugene T. McEnery.
Vice-President: Dr. Maxwell P. Borovsky.
Secretary: Dr. Ralph H. Kunstadter, 104 S. Michigan Blvd.
Treasurer: Dr. Noel G. Shaw.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Cincinnati Pediatric Society

President: Dr. John E. Allen, 2546 Auburn Ave.
Vice-President: Dr. Robert A. Lyon, Children's Hospital.
Secretary-Treasurer: Dr. William D. De Vaux, 7373 Brookcrest Dr.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Cleveland Academy of Medicine, Pediatric Section

Chairman: Dr. Robert Hauver, 10515 Carnegie Ave.
Secretary: Dr. William Herman, 10300 Carnegie Ave.

Corpus Christi Pediatric Society

President: Dr. Edwin A. Danford.
Secretary: Dr. Jack F. McKemie.
Place: As announced. Time: 7:30 p.m., fourth Wednesday of January, March, May, July, September, and November.

Dade County Pediatric Society

President: Dr. Lynn Whelchel, DuPont Bldg., Miami, Fla.
Secretary: Dr. Howard Engle, 311 Lincoln Rd., Miami Beach, Fla.

Dallas Pediatric Society

President: Dr. Floyd A. Norman, 4325 Cole Ave., Dallas.
Secretary-Treasurer: Dr. Charles L. Smith, 4207 Lemmon Ave., Dallas.
Place: Children's Hospital of Texas. Time: 6:30 p.m., first Thursday in each month.

Detroit Pediatric Society

President: Dr. Wolf Zuelzer.
Secretary: Dr. Mario S. Cioffari.
Place: Variable. Time: Five times a year.

Honolulu Pediatric Society

President: Dr. John Peyton, Medical Group, 1133 Punchbowl St.
Recording Secretary: Goonzo Yamashita, 1618 S. King St.
Corresponding Secretary-Treasurer: Dr. H. M. Sexton, Straub Clinic, 1020 Kapiolani St.
Place: At doctors' homes in rotation. Time: 6 p.m., third Thursday of each month.

Houston Pediatric Society

President: Dr. David Schrum, 5101 Fannin St., Houston.
Secretary: Dr. Juanita Thacker Hart, 306 South 7th St., Bellaire.
Place: River Oaks Country Club. Time: 6:30 p.m., fourth Tuesday of each month.

Kansas City Southwest Pediatric Society

President: Dr. Frank Hogue, Plaza Medical Bldg., Kansas City, Mo.
Secretary: Dr. S. J. Kranson, Truman Rd. and Ash, Independence, Mo.
Place: University Club, Kansas City, Mo. Time: On call.

Long Beach Pediatric Society

President: Dr. Kenneth Berkaw, 211 Cherry Ave., Long Beach, Calif.
Secretary: Dr. C. W. Latshaw, 3821 Atlantic Ave., Long Beach, Calif.
Place: Victor Hugo Restaurant, 730 E. Broadway. Time: First Tuesday night of every month.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Sidney Rosin, 6230 Wilshire Blvd., Los Angeles.
Secretary: Dr. Arthur J. Holmes, 65 N. Madison Ave., Pasadena 1.
Place: Los Angeles County Medical Association Bldg., 1025 Wilshire Blvd., Los Angeles. Time: Second Thursday of alternate months beginning in September.

Louisville Pediatric Society

President: Dr. Harry S. Andrews.
Vice-President: Dr. Joseph Little.
Secretary-Treasurer: Dr. Kenneth P. Crawford.
Place: Variable. Time: Five times a year, as announced.

Medical Society of the County of Kings and Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Jacob J. Lichterman, 1433 Union St., Brooklyn.
Secretary: Dr. Bernard Greenberg, 755 Ocean Ave., Brooklyn 26.
Treasurer: Dr. David Dragutsky, 1466 49th St., Brooklyn.
Place: Kings County Medical Society Auditorium, 1313 Bedford Ave., Brooklyn. Time: 8:45 p.m., fourth Monday of January, March, April, October, and November.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington 20.
Secretary: Dr. John E. Cassidy, 5402 Connecticut Ave. N.W., Washington.
Place: Medical Society Bldg., 1718 M St. N.W., Washington. Time: Spring and fall.

Memphis Pediatric Society

President: Dr. Clifton W. Woolley, 2448 Poplar Ave.
Vice-President: Dr. Steve H. Turnbull, 848 Adams.
Secretary-Treasurer: Dr. Charles H. Householder, 321 S. Bellevue.
Place: Rotated among four hospitals. Time: 7:30 p.m., second Tuesday of each month.

Milwaukee Pediatric Society

President: Dr. Franklin Mellencamp, 1513 E. Capitol Dr., Milwaukee.
Secretary: Dr. Karl Beck, 1411 Wauwatosa Ave., Milwaukee.
Place: Milwaukee University Club. Time: Second Wednesday of February, April, June, and October.

Mobile Pediatric Society

President: Dr. Daniel Sullivan, 1420 Government St., Mobile, Ala.
Secretary: Dr. Robert O. Harris III, 1514 Government St., Mobile, Ala.
Place: Admiral Semmes Hotel. Time: 7:30 p.m., fourth Thursday of September, November, January, March, and May.

Nashville Pediatric Society

President: Dr. Thomas Weaver, Bennie Dillon Bldg., Nashville, Tenn.
Secretary: Dr. Ethel Walker, 3415 West End Ave., Nashville, Tenn.
Place: Homes of members. Time: Third Thursday of every month.

Nassau Pediatric Society

President: Dr. Mildred Wicker Jackson, 254 South St., Oyster Bay, N. Y.
Secretary-Treasurer: Dr. David J. Posner, 98 Wolcott Rd., Levittown, N. Y.
Place: Felice's, Post Ave., Westbury, N. Y. Time: 7:30 p. m., second Monday of October, December, February, April, and June.

New York Academy of Medicine, Section on Pediatrics

Chairman: Dr. Jerome L. Kohn, 50 W. 96th St., New York 25.
Secretary: Dr. Lawrence B. Slobody, 1 E. 105th St., New York 12.
Place: New York Academy of Medicine, 2 E. 103d St. Time: 8:30 p.m., second Thursday of each month, November to May, inclusive.

Northern California Pediatric Society

President: Dr. Edward Campion, 707 C St., San Rafael.
Secretary-Treasurer: Dr. Joseph H. Davis, 300 Homer Ave., Palo Alto.
Place: San Francisco. Time: Quarterly, as speakers are available.

Oklahoma City Pediatric Society

President: Dr. C. M. Bielstein, 301 N.W. 12th St., Oklahoma City.
Secretary: Dr. Louis Frank, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: On call.

Philadelphia Pediatric Society

President: Dr. Charles C. Chapple, 1740 Bainbridge St., Philadelphia 46.
Secretary: Dr. F. H. Harvie, 133 S. 36th St., Philadelphia 4.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p.m., second Tuesday from October to May, inclusive.

Pittsburgh Pediatric Society

President: Dr. Christian John Stoecklein, 519 Medical Arts Bldg., Pittsburgh 13.
Secretary-Treasurer: Dr. James W. Stirling, 694 Lincoln Ave., Pittsburgh 2.
Place: Western State Psychiatric Institute and Clinic. Time: Second Friday in October, December, February, and April.

Queens Pediatric Society

President: Dr. Moe Goldstein, 111-32 76th Ave., Forest Hills, N. Y.
Secretary: Dr. John Finnegan, 36-19 Bowne St., Flushing, N. Y.
Place: Seminole Club, 112th St. and 70th Rd., Forest Hills, N. Y. Time: Second Tuesday in October, December, February, and April.

Richmond Pediatric Society

President: Dr. Hobart T. Dougan, 1832 Monument Ave., Richmond 20, Va.
Secretary: Dr. Robert A. Hoffman, 1001 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p.m., third Thursday of each month, except June, July, and August.

San Antonio Pediatric Society

President: Dr. Philip Magrish, 402 Fulton Ave.
Secretary: Dr. Jack M. Wright, 403 Summit Ave.
Time: 7:30 p.m., supper, first Tuesday of each month.

St. Louis Pediatric Society

President: Dr. H. E. Wachter, 8505 Delmar.
Vice-President: Dr. Raymond J. LaDriere, 35 No. Central, Clayton 5, Mo.
Secretary-Treasurer: Dr. Leo F. Gowen, 337 W. Lockwood, Webster Groves 19, Mo.
Place: Medart's Restaurant. Time: 7 p.m., second Thursday of each month from September to May, inclusive.

Santa Barbara Pediatric Society

President: Dr. Clarence B. Hills, 22B. W. Micheltorena St., Santa Barbara, Calif.
Secretary: Dr. Louise P. Brown, 3017 Foothill Rd., Santa Barbara, Calif.
Place: Varies. Time: Two to three times yearly, on call.

Seattle Pediatric Society

President: Dr. O. William Anderson.
President-Elect: Dr. Robert Tidwell.
Secretary-Treasurer: Dr. James L. Tucker.
Place: College Club. Time: 6:30 p.m., fourth Friday of each month from September to June.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Fred J. Chapin, 101 John St., Bay City.
Secretary-Treasurer: Dr. George H. Lowrey, University Hospital, Ann Arbor.
Place: University Hospital, Ann Arbor.

Waco Pediatric Society

President: Dr. J. M. Garrett, 1408 Austin Ave., Waco, Texas.
Secretary: Dr. C. G. Shellenberger, 1318 Austin Ave., Waco, Texas.
Place: 1917 Austin Ave., Waco, Texas. Time: Third Tuesday of each month.

Westchester County Medical Society, Pediatric Section

President: Dr. Herbert Kahan, 650 Main St., New Rochelle, N. Y.
Secretary: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Four dinner meetings a year, November, February, April, and June.

Western Michigan Pediatric Society

President: Dr. A. Morgan Hill, 310 Fulton, E., Grand Rapids.
Secretary: Dr. John C. Montgomery, 1810 Wealthy St., S.E., Grand Rapids.
Place: Two meetings in Grand Rapids, two elsewhere. Time: First Wednesday of October, November, April, and May.

Wichita Pediatric Society

President: Dr. Frank L. Menehan.
Secretary: Dr. R. C. Knappenberger.
Place: Homes of members. Time: 8:30 p.m., first Thursday, October through May.

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1. Cahill, W. M.: Schroeder, L. J., and Smith, A. H.: J. Nutrition 28:209, 1944. 2. Stoesser, A. V.: Ann. Allergy 4:404, 1944. 3. Schroeder, L. J.: Cahill, W. M., and Smith, A. H.: J. Nutrition 32:43, 1946. 4. Stoesser, A.V.: J. Allergy 18:29, 1947. 5. Clein, N. W.: Ann. Allergy 9:195, 1951. 6. Sternberg, S. D., and Greenblatt, I. J.: Ann. Allergy 9:190, 1951. 7. Sobel, S. H.: Clin. Med. 59:362, 1952. 8. Glaser, J., and Johnstone, D. E.: Ann. Allergy 10:433, 1952. 9. Stoesser, A. V., and Nelson, L. S.: Journal-Lancet 73:487, 1953. 10. Glaser, J., and Johnstone, D. E.: J.A.M.A. 153:620, 1953. 11. Johnstone, D. E., and Glaser, J.: J. Allergy 24:434, 1953. 12. Moore, I. H.: Journal-Lancet 74:80, 1954. 13. Speer, F.: Ann. Allergy 12:168, 1954.

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1. Watt, B.K., and Merrill, A.L.: Composition of Foods—Raw, Processed, Prepared, United States Department of Agriculture, Agricultural Handbook No. 8, 1950.
2. Data furnished by the Laboratories of The American Institute of Baking, Chicago, Illinois.
3. Sebrell, W.H., Jr.: Trends and Needs in Nutrition, J.A.M.A. *152*:42 (May 2) 1953.
4. Flour and Bread Enrichment, 1949-50, The Committee on Cereals, Food and Nutrition Board, National Research Council, 1950.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

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**Chick, H.: Nutrition 7:59, 1953; Cotereau, H. et al.: Nature 161:557, 1948. Jolliffe, N. et al.: Clinical Nutrition; Hoeber, New York, 1950; pp. 586-601.*

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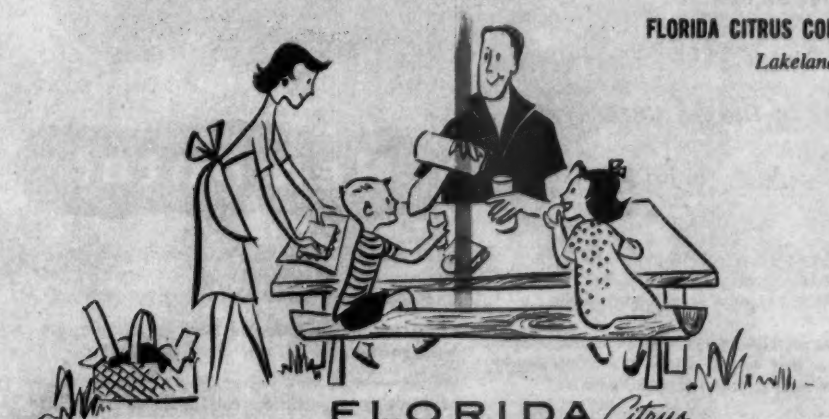

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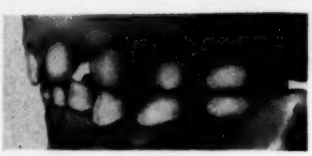

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THUM broke the habit and teeth returned to normal position in 9 months.

Get Thum at your druggist or surgical dealer. Prescribed by physicians for over 20 years.

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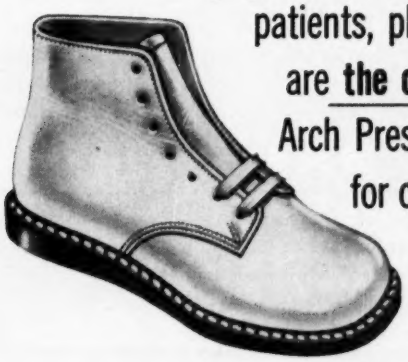
Selby*

JUNIOR ARCH PRESERVER

Shoes

* when you recommend shoes for your patients, please remember . . . Selby Juniors are **the only genuine** Arch Preserver Shoes for children



*Selby
JUNIOR ARCH PRESERVER SHOES

● *If Selby Junior Arch Preservers are not available in your city, please write directly to us.*

The Selby Shoe Company

Portsmouth, Ohio

MORE THAN THREE QUARTERS OF A CENTURY OF FINE SHOEMAKING

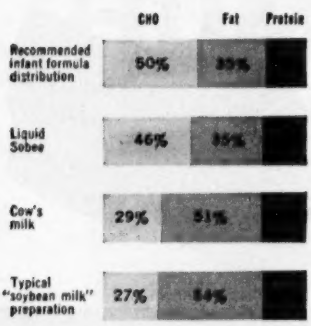
New...for allergic infants...

A NUTRITIONALLY UNEXCELLED FORMULA

LIQUID SOBEE

HYPOALLERGENIC SOYA FORMULA FOR INFANTS

COMPARATIVE CALORIC DISTRIBUTIONS



Liquid Sobee is far more than a mere "soybean milk." It is a well balanced infant *formula* designed to promote optimum growth and development in infants who cannot take milk. Liquid Sobee® does not cause the diarrheas so often associated with "milk substitutes." Well tolerated even by young infants, it can be prescribed without hesitation for temporary or prolonged use.

Liquid Sobee's caloric distribution is based on authoritative recommendations for infant *formulas*—not on the proportions of milk. The infant is assured a generous intake of protein of high biologic value. Protein-sparing and caloric needs are met with well tolerated, easily metabolized fat and adequate added carbohydrate.

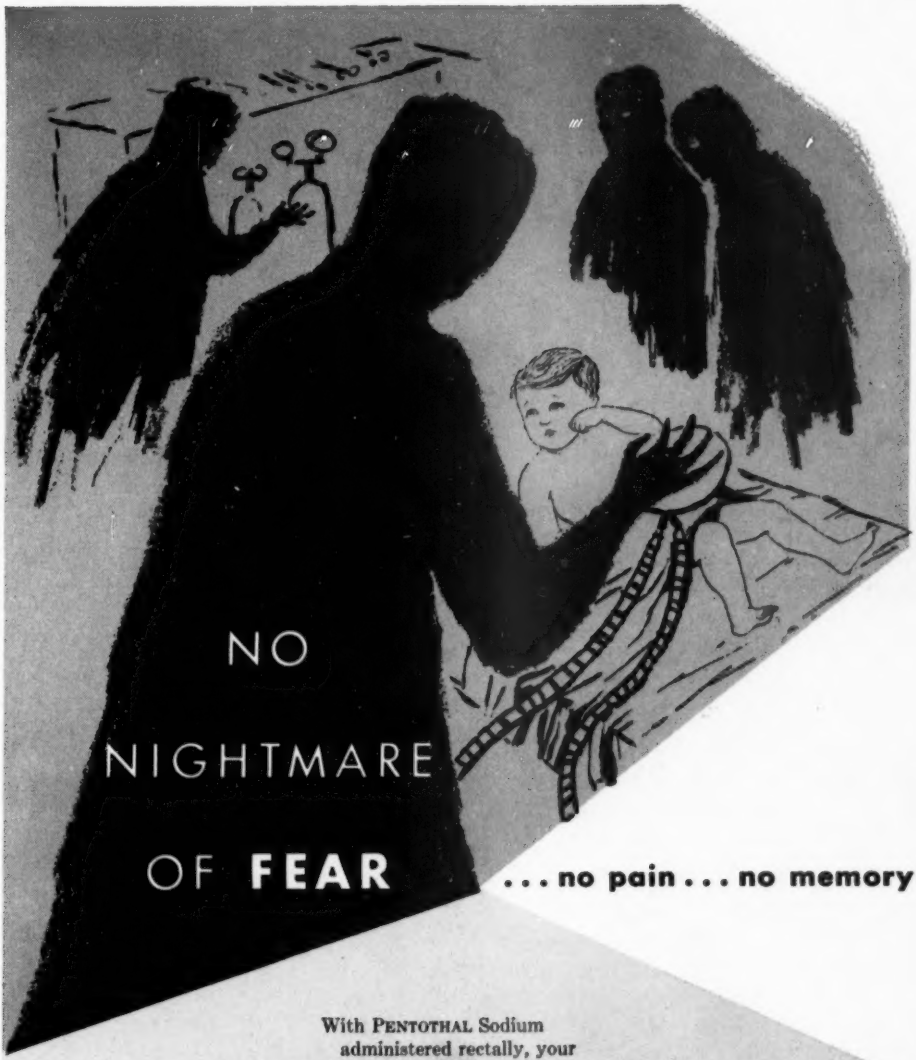
Mead's new and dramatically different processing methods prevent the usual destruction of important natural B vitamins and amino acids. Liquid Sobee contains 4.8 mg. iron per quart of normal dilution.

Physically superior...easy to use

- **Tastes good . . . no "burned" flavor**
- **Looks good . . . light and appealing**

Easy to prepare: 1 part Liquid Sobee to 1 part water for a hypoallergenic formula supplying 20 calories per fluid ounce.

MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA, U.S.A. MEAD



NO NIGHTMARE OF FEAR

. . . no pain . . . no memory

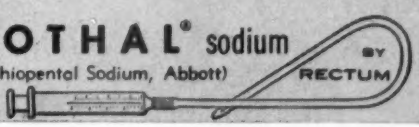
With PENTOTHAL Sodium administered rectally, your pediatric patients have no awareness of the operating room, no memory of the experience. Instead, they drop off to sleep in the security of their own rooms before surgery and awake there afterward. Controlled, individual dosages may be given to attain levels ranging from preanesthetic sedation to basal anesthesia. Rectal PENTOTHAL offers a wide margin of safety. In many short, minor procedures, Rectal PENTOTHAL may serve as the sole agent. When general anesthesia is desired, Rectal PENTOTHAL reduces the dosage of inhalation agents. Abbott

Send for literature— "...PENTOTHAL Sodium by Rectum" results from nearly 4,000 cases. Write Abbott Laboratories, North Chicago, Illinois.

PENTOTHAL® sodium

(Sterile Thiopental Sodium, Abbott)

BY RECTUM



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Steadily assimilated carbohydrates

Widespread clinical experience has established Cartose as a valuable modifier of milk in any form.

Cartose contains a mixture of carbohydrates—dextrins, maltose and dextrose—each having a different rate of assimilation.

Added to the infant's formula, Cartose assures a steady absorption of carbohydrate with a corresponding low rate of fermentation and low incidence of digestive disturbances.

CARTOSE®

MIXED CARBOHYDRATE in easy-to-use liquid form

- ...ly soluble
- ... clogging
- ... OF 1 PINT
- ...ula blanks
- No gumming
- No caking

Milk Diffusible Vitamin D_2

DRISDOL®

IN PROPYLENE GLYCOL

Sterile clear solution of pure crystalline vitamin D_2—10,000 U. S. P. vitamin D units per gram, 250 units per drop. Indefinitely stable. Bottles of 5 cc., 10 cc. and 50 cc.

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